

# GROWTH

## Genetics & Hormones

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### The Fetal Alcohol Syndrome

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The fetal alcohol syndrome is a pattern of altered growth, structure, and function in the offspring of chronically alcoholic women who continue to drink heavily throughout pregnancy. Since the initial delineation of this condition in 1973, it has become clear that prenatal alcohol exposure can lead to a variable spectrum of defects. At the most severe end is an increased frequency of fetal wastage; less severely affected children manifest prenatal onset of growth deficiency, mental retardation, and facies characteristic of fetal alcohol syndrome, while the most mild end of the spectrum includes otherwise normal children with learning disorders and mild growth deficiency.

#### Incidences

Since children at the most mild end of the spectrum are frequently not identified as being prenatally affected by alcohol, the true incidence of this syndrome is difficult to determine. In a study conducted in Goteborg, Sweden, Olegard et al estimated the incidence of the full-blown fetal alcohol syndrome to be one in 600 liveborn infants, while one in 300 had partial or milder manifestations of the syndrome. In the United States, the fetal alcohol syndrome is thought to be the third most common recognizable cause of mental retardation, with an incidence of one to two per 1000 live births. However,

in areas where maternal alcohol abuse is high, the incidence of the fetal alcohol syndrome is far higher.

#### Pattern of Malformation

Features most frequently seen in children with the fetal alcohol syndrome are listed in the table and are further described below.

#### Growth

Prenatal and postnatal growth deficiency occur in the vast majority of affected individuals. In the first eight patients reported to have this disorder, mean gestational age was 38 weeks, while birth length and weight were in the 50th percentile for gestational ages of 33 and 34 weeks, respectively. Regarding postnatal growth, a follow-up study of the same eight children, plus three additional children also reported to have the fetal alcohol syndrome, indicates continued growth deficiency with respect to both length and weight over a ten-year period. Although some degree of catch-up linear growth during the first 1½ years of life was evident in most patients, weight decreased during the

same time period for the majority. Thereafter, length remained relatively constant while catch-up growth occurred with respect to weight. Initially, all the children were strikingly underweight for their length, with a weight-for-height age in the preschool years averaging between the fifth and tenth percentile. However, with the onset of puberty, two of the three females had become overweight for height; the weight of the third pubertal girl was appropriate for her height age.

With respect to brain growth, head circumference, which at birth was below the third percentile for gestational age in the vast majority of patients, decreased relative to height age during the first one and 1½ years. Thereafter, head circumference remained two to four standard deviations below the mean for chronologic age in the majority of patients.

The etiology of the growth deficiency seen in this disorder is unknown. Tze et al evaluated five patients and found a normal or slight hyper-response of growth hormone (GH) and normal somatotropin activity in those samples with high GH levels. Normal function of the hypothalamic-pituitary axis was seen in four additional affected children studied by Root et al. These findings suggest that the growth deficiency is not due to hormonal factors.

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#### Performance and Central Nervous System Defects

Of greatest significance is the effect that prenatal alcohol exposure can have on brain development. Although the average IQ of children with fetal alcohol syndrome is

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63, a wide range of developmental outcomes has now been documented. At one end are children with profound mental deficiency and cerebral palsy; at the other are those with normal intelligence who manifest learning disorders and other behavioral aberrations.

Characteristic neuropathologic findings noted in the brains of some affected children include multiple heterotopias throughout the leptomeninges and cerebral mantle resulting from aberrations of neuronal migration. Meningocele and hydrocephalus have also been seen, but in extremely small numbers.

### Facies

Many of the characteristic facial features of the fetal alcohol syndrome are believed to be a function of the effect of alcohol on early brain development. For example, since the optic vesicles that develop as evaginations from the neural ectoderm are responsible for induction of normal palpebral fissures, it is suggested that alcohol-related defects of brain development—and thus optic vesicle development—lead secondarily to an alteration in palpebral fissure size. In addition, it has been suggested by Sulik et al, who utilized a prenatally exposed mouse model, that the long, smooth phil-

trum and thin vermillion of the upper lip are secondary to a defect in forebrain development resulting in closely set olfactory placodes and underdeveloped medial nasal processes. Since the medial nasal processes form the columella, the philtrum, the portion of the dentalveolar ridge containing the upper incisors, and the anterior portion of the hard palate, Sulik suggested that deficiency of the medial nasal processes leads to fusion of the maxillary processes at the midline to form the characteristic long philtrum seen in children with the fetal alcohol syndrome.

### Skeletal Defects

Many of the skeletal defects seen in this condition are also due to the effect of alcohol on brain development. For example, since joint development depends on fetal activity, the joint contractures seen in affected children are secondary to decreased fetal activity and decreased joint mobility. Similarly, since development of palmar crease patterns depends on movement of the hands, the altered palmar crease patterns are secondary to the effect of alcohol on early development of the brain.

### Cardiac Defects

Of the 76 children with the syndrome who were diagnosed by Smith et al, 31 had a cardiac defect, and an additional 12 had

functional murmurs. Although only three of the 15 children with isolated ventricular septal defects required surgery, ten of the 16 children with complex cardiac defects required or had undergone surgery at the time the report was published (1981).

### Other Defects

Other defects that become significant as the child grows older include dental malalignment and malocclusions, eustachian tube dysfunction, and myopia. The incidence of renal anomalies is unclear. Intravenous pyelograms in 19 affected children revealed two with ureteropelvic obstruction, one with a neurogenic bladder secondary to meningocele, and one with malrotation of one kidney.

### Etiology and Pathogenesis

Despite numerous studies in humans and laboratory animals, no clear-cut explanation of the pathogenetic mechanisms and risk factors associated with the fetal alcohol syndrome has yet been demonstrated. Although it is becoming increasingly clear that the occurrence of the fetal alcohol syndrome cannot be predicted by alcohol consumption alone, a crude dose-response effect has begun to emerge. Based on a number of retrospective and prospective studies, the incidence of serious problems in the offspring of alcoholic women who continue to drink heavily throughout pregnancy ranges from 30% to 50%. Moderate alcohol consumption—defined as one to two ounces of absolute alcohol per day (two to four ounces of whiskey or two to four glasses of wine)—has been associated with an 11% incidence of babies who show evidence of the adverse prenatal effect of alcohol. The extent to which lesser amounts of alcohol at various times during pregnancy can cause problems in fetal development is unknown. However, the full-blown fetal alcohol syndrome has not been seen in babies born to women who drink less than one ounce of absolute alcohol per day.

Variables other than the amount

**Table.** Pattern of Malformation

**Growth:** Prenatal and postnatal growth deficiency

**Performance:** Developmental delay; fine motor dysfunction manifested by weak grasp and poor eye-hand coordination; irritability, hyperactivity, and poor attention span; speech problems

**Craniofacial:** Microcephaly; short palpebral fissures; ptosis; maxillary hypoplasia; long, smooth philtrum; thin vermillion of upper lip

**Skeletal:** Joint alterations, including camptodactyly, flexion contractures at elbows, congenital hip dislocations, and foot positional defects; radioulnar synostosis; tapering terminal phalanges, with hypoplastic fingernails and toenails; cervical spine abnormalities; altered palmar crease pattern

**Cardiac:** Ventricular septal defect; atrial septal defect

**Other:** Cleft lip, palate or both; myopia; strabismus; epicanthal folds; dental malocclusion; hearing loss; protuberant ears; abnormal thoracic cage; renal anomalies; strawberry hemangioma; hypoplastic labia majora

of alcohol consumed may be important in the expression of the fetal alcohol syndrome. These include parity, socioeconomic status, smoking, marital status, use of other drugs, and altered placental function.

Recently, an animal model has been utilized to evaluate the genetic background of the mother and the developing fetus. Using three inbred strains, Chernoff demonstrated that the incidence of malformations in the offspring of alcoholic mice was dependent on the genetically determined rates of maternal alcohol metabolism, as well as on the amount of alcohol consumed. This study implies that the incidence of the fetal alcohol syndrome is dependent upon the maternal genotype as well as on the maternal consumption of alcohol.

That the fetal genotype may also play an important role in humans is suggested by the documentation of discordance for the fetal alcohol syndrome in dizygotic twins. Evidence in humans of a genetic contribution to alcohol metabolism has been documented. Moreover, Veghelyi and co-workers demonstrated elevated blood acetaldehyde levels in a chronic alcoholic woman who had previously given birth to a child with the fetal alcohol syndrome. The elevated levels, compared to levels from three normal, nonalcoholic controls, gave further credence to the concept that differences in maternal alcohol metabolism are important determinants of the fetal alcohol syndrome.

To test further the hypothesis that susceptibility to the fetal alcohol syndrome is dependent on genetic differences that result in differences in maternal alcohol and acetaldehyde metabolism or both, Cooper et al monitored breath alcohol and acetaldehyde levels for 240 minutes following administration of 0.75 cc of 95% ethanol/kg body weight in five nonpregnant alcoholic women who had given birth to affected babies, five non-pregnant alcoholic women who had given birth to normal babies, and five nonalcoholic controls. Al-

though no statistically significant differences among the three groups of women could be documented, a trend towards elevated alcohol and acetaldehyde levels in the group of alcoholic women who gave birth to affected babies was demonstrated. This trend was strongest during the first 120 minutes after ingestion.

Although the data do not provide any concrete information regarding pathogenesis of the fetal alcohol syndrome, a recent study has documented two factors that may be helpful in predicting the ultimate prognosis for affected children. Of greatest importance is the extent and severity of the pattern of malformation, including the growth deficiency. Those children noted during the newborn period as being severely affected were noted at follow-up to have the most severe degree of microcephaly, the shortest stature, and the most impaired intellectual function. Next in importance is the severity of the maternal alcoholism. Three of the four mothers with the most seriously handicapped children who were followed for ten years by Streissguth et al died of alcohol-related causes within six years after giving birth to their affected children.

### Conclusion

Despite the fact that alcohol has now clearly been identified as a significant human teratogen, a number of practical questions remain unanswered. Foremost among them is the extent to which lesser amounts of alcohol (one ounce or less per day) can affect fetal development. Pregnancy outcome associated with lesser amounts of alcohol is difficult to study since many of the more subtle effects of prenatal alcohol exposure may involve learning disorders that often do not become obvious until a child reaches the first grade in school. At present, it is important to recognize that no study has established a "safe" amount of alcohol for all pregnant women. Depending on unknown factors, which may well be genetically determined, what may be a

"safe" amount of alcohol for some women may have devastating effects on the unborn babies of others. Therefore, it is the author's belief that total abstinence from alcohol is the best policy throughout pregnancy.

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# Human Placental Lactogen and Fetal Growth

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Placental lactogen, or chorionic somatomammotropin, is a protein hormone of the placenta that has striking chemical and biologic homologies to growth and prolactin. Early studies of the physiology of placental lactogen focused primarily on the biologic actions of the hormone in the mother, while more recent studies have focused on the actions of the hormone in the fetus. This presentation will deal predominantly with investigations of the action of placental lactogen action in the fetus that strongly suggest a direct role for the hormone in the regulation of fetal growth and metabolism. In addition, some recent studies of secretion of placental lactogen will be presented; these studies implicate the involvement of several novel factors in the regulation of release of this placental hormone.

## Physiologic Studies of Placental Lactogen

In the pregnant woman, human placental lactogen (hPL), like growth hormone (GH), has been shown to induce peripheral insulin resistance, elevate blood glucose and amino acid concentrations, and stimulate insulin secretion. Some studies have also shown that hPL stimulates lipolysis. Since these metabolic actions of hPL are qualitatively similar to those of GH, and since plasma hPL concentrations increase markedly during gestation (while GH concentrations do not change), many investigators have suggested a major role for hPL as a maternal "growth hormone" of the second half of pregnancy. Although the effects of the increase in maternal hPL concentrations on the fetus are unknown, the resultant changes in maternal substrate concentrations may promote the transport of nutrients to the fetus and thereby stimulate fetal growth.

Because concentrations of placental lactogen in maternal serum greatly exceed the concentration of placental lactogen in umbilical cord blood, the effects of placental lactogen on fetal metabolism were felt to be mediated only indirectly by changes in maternal metabolism and not by direct effects of the hormone on fetus tissues. However, with the recent demonstration that placental lactogen has direct growth-promoting actions in the fetus, it appears that placental lactogen may affect fetal growth *by promoting substrate transport to the fetus and by acting directly on fetal tissues*.

Initial studies of placental lactogen action in fetal tissues focused on the biologic actions of ovine placental lactogen (oPL) in fetal rat and sheep tissues. oPL was shown to stimulate dose-dependent increases in amino acid transport into fetal rat skeletal muscle and glycogen accumulation in fetal sheep and rat hepatocytes. The increase in hepatic glycogen content resulted from both stimulation of glycogen synthesis and inhibition of glycogenolysis. Although GH stimulated amino acid transport in postnatal skeletal muscle, GH had no effect on amino acid transport in the fetus, even at concentrations considerably greater than the half-maximal effective concentration of oPL. In addition, the potency of GH in stimulating glycogen synthesis in fetal hepatocytes was only about one tenth that of oPL. These studies indicate that placental lactogen has metabolic actions in the fetus and that GH has little or no metabolic activity in fetal tissues. Since the biologic actions of placental lactogen in the fetus are qualitatively similar to those of GH in postnatal animals, these studies further support a role for placental lactogen as a fetal "growth hormone."

The lack of somatotropic and metabolic activity of GH in the fetus is in accordance with other clinical and experimental observations suggesting that GH does not

play a central role in the regulation of fetal growth. For instance, a deficiency or absence of GH in the mammalian fetus does not limit fetal weight gain or linear growth *in utero* and does not reduce fetal plasma somatomedin concentrations. Furthermore, an excess of fetal GH, as noted in transgenic mice bearing metallothioneine-hGH fusion genes, does not accelerate fetal growth.

In additional studies, oPL has also been observed to stimulate the activity of ornithine decarboxylase (ODC) in the fetal liver directly. Since ODC is the rate-limiting enzyme in the synthesis of the polyamines, a group of compounds that play a critical role in the regulation of protein and in nucleic acid metabolism, this finding further supports a direct role for placental lactogen in the regulation of fetal growth. In contrast, GH, which stimulates ODC activity in the postnatal liver with a potency identical to that of oPL, has no effect on fetal hepatic ODC activity.

OPL at physiologic concentrations has also been shown to stimulate an increase in dose-dependent, insulin-like growth factor-II (IGF-II) synthesis in fetal rat embryo fibroblasts, while GH and a variety of other hormones were found to have no effect. However, when tested in fibroblasts from postnatal rats, both oPL and GH stimulated the synthesis of IGF-I but not IGF-II. Since the plasma concentration of IGF-II in the fetal rat and lamb greatly exceeds that of IGF-I, these studies suggest that fetal growth may be regulated, in part, by oPL through its actions on the synthesis of fetal IGF-II. Additional support for a role of placental lactogen in fetal growth comes from recent studies indicating that hPL stimulates somatomedin production, DNA synthesis, and amino acid transport in human fibroblasts and myoblasts. The table summarizes the evidence supporting a role for placental lactogen.

**Table.** Evidence suggesting a direct role for placental lactogen in fetal growth and development

- Placental lactogen detected in human, ovine, and bovine fetal sera
- Distinct placental lactogen receptors demonstrable in fetal tissues
- Placental lactogen has anabolic effects on fetal amino acid and carbohydrate metabolism and stimulates somatomedin production in fetal tissues
- Low levels of hPL in cord blood may be associated with intrauterine growth retardation

Placental lactogen competes with GH and prolactin for binding to GH and prolactin receptors in mammalian postnatal tissues. Consequently, several investigators have suggested that the metabolic effects of placental lactogen may be mediated through binding to GH or prolactin receptors or both. However, the studies demonstrating marked differences in the potencies of oPL and ovine GH (oGH) in fetal tissues strongly suggest that there are distinct placental lactogen receptors in the fetus.

The presence of distinct receptors for placental lactogen in the fetus is further substantiated by more recent studies. Ontogenetic studies of the binding of placental lactogen and GH to hepatic membranes of fetal sheep indicate the presence of specific oPL binding sites as early as mid-gestation, with a marked increase in the number of oPL binding sites during the latter half of gestation. Specific binding for GH, on the other hand, does not appear until shortly after birth. Biochemical studies of the hepatic membrane receptors for oPL and oGH also indicate striking differences in the binding sites of the two hormones. oPL binds to a single binding site in fetal hepatic membranes; the binding site has an apparent molecular weight by SDS-PAGE of 38-43 kD. In contrast, neither GH nor prolactin binds to fetal liver membranes. In hepatic membranes from postnatal sheep, the GH receptor appears to be a complex of disulfide-linked subunits with apparent molecular weights of 53 and 118 kD. Thus, the GH receptor in the postnatal sheep liver is structurally distinct from the

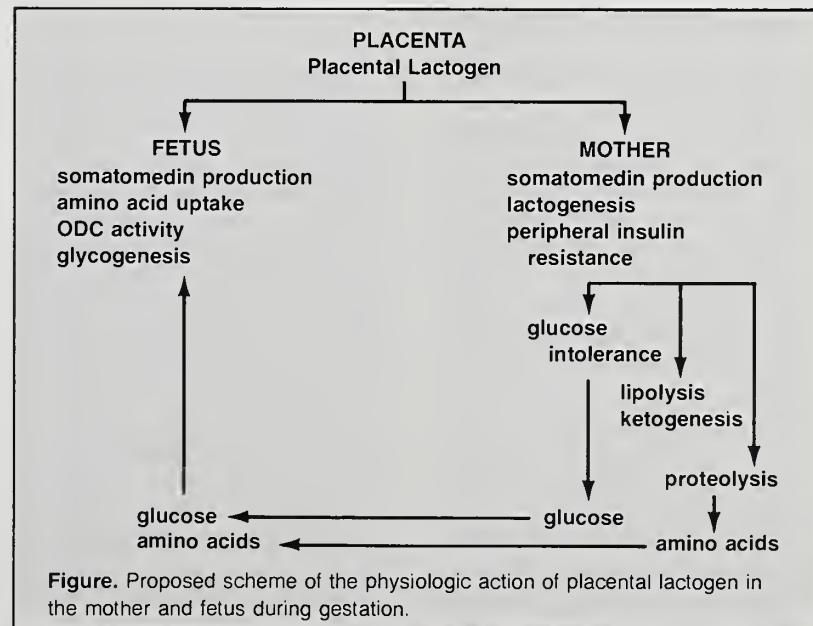
placental lactogen receptor in the fetal liver. These observations strongly suggest that a new and structurally distinct GH receptor appears soon after birth in the sheep.

In summary, placental lactogen appears to have numerous metabolic effects in the mother and fetus and these effects promote fetal growth (Figure). In the mother, placental lactogen induces insulin resistance and stimulates lipolysis and proteolysis, biologic effects that promote the transfer of glucose, amino acids, and to a lesser extent, fatty acids to the fetus. In the fetus, placental lactogen acts directly to stimulate ODC activity, somatomedin production, glycogen accumulation, and amino acid transport into cells. Since fetal tissues contain specific receptors for placental lactogen, and since the biologic actions of placental lac-

togen in fetal tissues occur at physiologic concentrations, the effects of placental lactogen on fetal growth appear to result from a concerted action of the hormone on both maternal and fetal tissues.

The observation that women with very low hPL concentrations resulting from a deletion of two of the three genes coding for hPL have normal pregnancies and give birth to normal-sized babies indicates that placental lactogen is not the only hormonal factor involved in the regulation of fetal growth. Since fetal growth, like postnatal growth, is undoubtedly controlled by many factors, the low hPL concentrations in the fetus may have resulted in compensatory changes in GH and other factors involved in somatomedin production. One possible explanation for normal fetal growth in pregnant women with gene deletions for hPL comes from the recent studies of Frankenne et al. These studies demonstrate that the placentas from these pregnancies may produce hPL-like or hGH-like molecules through expression of placental genes that are not expressed under normal conditions. It is possible that these hPL-like or hGH-like gene products may assume hPL-like roles in the mother or the fetus or both, sus-

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**Figure.** Proposed scheme of the physiologic action of placental lactogen in the mother and fetus during gestation.

## Human Placental Lactogen

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taining normal fetal growth and development during those pregnancies complicated by a deficiency or an absence of normal hPL production. It is also possible that low hPL concentrations during pregnancy may cause an up-regulation of hPL receptors or an increase in the affinity of the hPL receptor or both.

### Regulation of hPL Release

Because the chemical and biologic properties of placental lactogen are very similar to those of GH, initial investigations to delineate the factors regulating the release of hPL focused on factors known to regulate the release of GH. In these studies, hyperglycemia and insulin-induced hypoglycemia produced no consistent effects on plasma hPL concentrations, and growth hormone-releasing factor and somatostatin had no effect on hPL release. These results, therefore, strongly suggest that the regulation of placental lactogen re-

lease is different from that of GH.

Recently, an hPL-releasing factor that selectively stimulates the release of hPL has been partially purified from the serum of pregnant women. Chemical investigations to date indicate that the releasing factor is a protein with an apparent molecular weight of approximately 28,000. However, the amino acid composition and sequence of the protein and its site of origin are unknown. HPL release has also been shown to be stimulated by high-density lipoproteins (HDL). However, unlike the actions of HDL in other tissues, the stimulatory effect of HDL on placental lactogen release is not due to the lipid constituents of HDL but is due to apolipoproteins AI, AI, and CI. Since human placental tissue contains specific receptors for HDL, and plasma HDL concentrations increase progressively during pregnancy with a pattern similar to that of hPL, these studies strongly suggest a physiologic role for HDL in the regulation of hPL release.

IGF-I has also been recently demonstrated to stimulate hPL re-

lease from human placental explants. Since the human placenta synthesizes IGF-I and placental plasma membranes contain specific IGF-I receptors, it is possible that somatomedin may also be involved in the regulation of hPL release. These findings indicate a complex interaction of hormones, growth factors, and nutrients in the regulation of maternal metabolism, placental function, and fetal growth.

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# Creutzfeldt-Jakob Disease: Current Reports and Comments

Robert M. Blizzard, M.D.

Chairman, Editorial Board

*Growth, Genetics, and Hormones*

There has been much concern since the association between Creutzfeldt-Jakob disease (CJD) and pituitary growth hormone (GH) was first reported. Two recent reports—"Human Growth Hormone Therapy and Creutzfeldt-Jakob Disease: A Drama in Three Acts" (Brown, P. *Pediatrics* 1988; 80) and "Iatrogenic Creutzfeldt-Jakob Disease" (Rappaport, E. *Neurology* 1987;37:1520)—deserve special comment.

Dr. Brown, author of the first report, is a virologist and epidemiologist who has worked at the NIH for many years with Dr. Carlton Gadjusek and other pioneers who study kuru, CJD, and other brain diseases attributed to long-acting

viruses. Dr. Rappaport, a pediatric endocrinologist, wrote the second report. She became involved in CJD research while serving as a medical officer for the United States Food and Drug Administration.

Dr. Brown's article is derived from the Lawson Wilkins Lecture, which he delivered in the spring of 1987 at the Lawson Wilkins Pediatric Endocrine Society meeting. Dr. Brown records the events that prompted the termination of distribution of native growth hormone (GH), reviews epidemiologic studies that are currently under way as a follow-up to the initial report of three patients who received GH many years before their deaths from CJD in 1985, and reports four

additional cases of CJD—two abroad and two in the United States. He also reports two other patients who received native GH and who have a cerebellar syndrome, but whose histories and clinical courses suggest that their disease may be different from CJD, although the possibility of CJD cannot be ruled out completely.

There are, therefore, seven proven cases of CJD worldwide among patients who received GH many years ago (five in the United States, one in New Zealand, and one in England). Six have had clinical disease with pathological confirmation and the seventh had one brain lesion consistent with CJD

identified at autopsy, although the death was due to other causes. All except the British patient received pituitary GH prepared in the United States between 1966 and 1969. A review of laboratory records indicates that one batch of pituitary glands harvested in 1966 had found its way into at least one lot of the GH preparation given to the five American patients. However, this batch could not be incriminated as the cause of CJD in the patients from England and New Zealand. Priority has been given to a search for all recipients of the early lots of pituitary GH.

Studies in animals given injections of GH prepared from the early batches have not revealed deaths attributable to CJD but, unfortunately, negative results do not necessarily demonstrate freedom from contamination.

Dr. Brown believes that the possibility of a major epidemic of iatrogenic CJD seems less and less likely, and a reasonable guess is that the final tally will be perhaps 15 to 20 cases, with an occasional case reported over the next two decades. Epidemiologic studies are under way. The endocrinologic, social, psychologic, and medical data that will be obtained from them will go beyond data that are used for the prospective and retrospective study of the incidence of CJD.

In reply to an inquiry from me in late October, 1987, Dr. Brown said that there were no additional known cases of CJD and that the two patients with cerebellar syndrome were alive. He also stated that the epidemiologic studies are progressing and that the animal studies are continuing.

Dr. Rappaport focused on the transmission of CJD in her article. In addition to transmission via injections of GH, CJD has been inadvertently transmitted during surgical procedures, particularly those necessitating grafts of tissue, placement of electrodes in the brain, or both. In animals, CJD has been transmitted via the blood and urine of infected patients. Apparently, the infecting agent can be present in the blood and urine

of asymptomatic patients. If so, the risk of the iatrogenic spread of CJD will be proportional to the prevalence of potentially infectious people in the population. Dr. Rappaport calculates the possible prevalence in different ways, and depending on the assumptions used, the prevalence of the carrier state may be considerable.

On the basis of this possibility, Dr. Rappaport makes several recommendations:

(1) The medical community needs to be made aware of the potential infectivity of tissue and body fluids obtained from patients with CJD and of the potentially significant increase in the number of people who may be harboring the CJD pathogen.

(2) Hospitals should routinely review their sterilization procedures for surgical instruments and operating suites and their procedures for decontamination of the CJD pathogen. These should comply with current recommendations for inactivation of the CJD agent.

(3) Epidemiologic studies in patients exposed to native GH should include a tabulation of the surgical procedures performed before and after GH therapy.

(4) Consideration should be given to prohibiting recipients of pituitary-derived GH from donating blood, tissue, or organs.

(5) Regulations should be instituted to minimize the chance of manufacturing biologic products from the blood, tissue, or organs of individuals who may harbor the CJD pathogen.

Summaries of these articles are presented to update our readers about CJD. I asked Dr. Judith Fradkin to comment further. As Chief of the Division of Endocrinology and Metabolic Diseases, Program Branch, at the National Institute of Diabetes and Digestive and Kidney Diseases, she is responsible for coordinating many of the ongoing CJD studies that are sponsored by the NIH.

#### **Dr. Fradkin's comments:**

Clearly, recipients of pituitary GH are at increased risk for CJD. The extent of the risk will be better un-

derstood after the epidemiology study is complete. However, a comparison of the number of cases of CJD identified in GH recipients in the United States (five over several years) with the total number of cases of CJD in the United States (142 deaths in 1980) suggests that cases associated with GH administration will constitute a small fraction of the total number of cases of CJD in America. Thus, while there is the *potential* for a significant increase in the number of people harboring the CJD pathogen, current experience indicates that GH administration is unlikely to have increased the prevalence significantly. Because recipients of pituitary GH are at increased risk for CJD, and because there is no test to detect infection, and because CJD may be transmitted through blood or tissue, these individuals should not serve as blood or tissue donors. Patients and physicians have been notified of this recommendation, and blood banks will not collect blood from pituitary GH recipients. The routine precautions currently recommended to protect medical personnel from exposure to body fluids and tissues of patients with certain infectious disease should be sufficient to protect against the CJD pathogen and similar infectious agents. There are no additional special precautions for health care workers who treat recipients of pituitary GH. It is also reassuring that household contacts, including spouses of persons who have CJD, have not been at increased risk for infection. Thus, we do not recommend that a person who has received pituitary GH make any changes in social or family interaction.

The epidemiology study is well under way. Identification of the cohort that received pituitary GH through the National Hormone and Pituitary Program is nearly complete. The questionnaire to be administered has been developed under the guidance of an advisory panel. The study is designed to determine the incidence of CJD in the cohort and the association of CJD with specific lots of hormone;

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**Creutzfeldt-Jakob Disease:**  
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to identify other possible adverse outcomes associated with GH deficiency or therapy; and to determine the long-term outcome of this cohort in terms of pituitary function, psychosocial development, and final height. The telephone survey will begin early in 1988 and

will be completed by the end of the year. Medical records and available neuropathologic specimens are being obtained and reviewed for all deceased patients who were identified through the National Death Index and subsequently through the survey. No cases of CJD have been identified through the epidemiology study other than the five already described.

**Editor's note:** A fact sheet on human growth hormone and CJD and a reference list of the scientific literature in this area may be requested from:

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**Special Report: International Turner Syndrome Symposium—**  
**November 9-11, 1987, San Francisco, California**

Robert M. Blizzard, M.D.  
*Chairman, Editorial Board*  
and Judith G. Hall, M.D.  
*Associate Editor*  
*Growth, Genetics, and Hormones*

Several aspects of Turner syndrome—including its natural history, therapy of short stature, and intellectual and psychosocial development—were discussed at this five-session symposium.

During one session on the genetics, organogenesis, and incidence of Turner syndrome, much attention was directed to the genes found on the X and Y chromosomes. Portions of that session are highlighted in this report.

Dr. L. Shapiro (University of California, Los Angeles) discussed an area of complete homology on the tips of the p (or short) arm of the X and Y chromosomes. This region, called the "pseudoautosomal region," escapes inactivation in the inactivated X chromosome. Currently, two functional genes are known to exist in this region: a steroid sulfatase gene in mice and a MIC 2 (surface antigen) in human beings. The pseudoautosomal region has 5-7 megabases. There is room for several hundred as yet undefined genes in this region.

Dr. C. Epstein (University of California, San Francisco) emphasized that aneuploidy is a disorder of gene dose and that gene dosage effects may perturb structure, function, or both. The Y chromosome carries a gene or genes for sex determination and prevents Turner syndrome. The "inactive" X chromosome does not have inac-

tivation of the pseudoautosomal region. Regions of the X chromosome appear to have an oocyte-maintaining function, as there are families whose members have premature menopause associated with minor deletions of the X chromosome. Dr. Epstein suggested that the Y chromosome be inspected for genes that affect somatic development because the Y chromosome is much easier to study than the X in many respects. He described two phenotypic females (karyotype 46, XY) with lymphedema who had minor deletions of the Yp.

The intrauterine mortality of 45, X fetuses is 95% to 99%, but death does not necessarily result from fetal defects; however, death could occur because of an abnormal placental karyotype. Interestingly, the paternal X is lost more frequently than the maternal X in Turner syndrome, and the paternally derived X is more likely to be the inactivated X in 46, XX individuals.

Dr. D. Page (Massachusetts Institute of Technology) hypothesized that a single gene on the Y chromosome, known as the gene for testicular differentiating factor (TDF), is sex determining. Its locus is on the p arm just proximal to the pseudoautosomal region. The question was raised as to whether a similar region is also present on the X chromosome. If the TDF gene is present on both the X and Y chromosomes, testicular differentiation alternatively could be an effect of gene dosage and not necessarily due to one gene on the

Y chromosome. Of 26 XX males studied, 24 had Y material on the X chromosome. These 24 may have had XY interchange at paternal meiosis of the sperm.

Among the 155 46,XY individuals with Y deletions who were studied, there were nine subgroups based on mapping of the missing loci on the Yp. Of the 24 XX males with Y material, all had Y region 1A2 present. This region, which appears to be critical for male differentiation, was "lost" in 46, XY females. The TDF gene is not the gene for the HY antigen since the two map to different areas of the Y chromosome; HY antigen maps to the 4B region of Yp. The TDF does not code for a hormone but rather for a DNA-binding protein. Dr. Page postulated that the two XX males without identifiable Y material, of the 26 XX males studied, may have a mutation of another gene, possibly an autosome.

An extension of this type of study was reported by Dr. C. Disteche (University of Washington), who used cytogenetic assays and DNA probes to study XY females who were not short. A deletion of the TDF loci area was identified. The area on Yp, which is believed to account for the short stature seen in Turner syndrome, is therefore not the TDF loci.

Dr. Disteche also discussed the seven regions on the Y chromosome. Region 7, a long segment at the distal end of the long arm, is brightly fluorescent. Its deletion does not produce significant problems, although two patients

with a small Y had small teeth and petite bones. Stature was unaffected. The development of gonadoblastoma in those patients with Turner syndrome who have a partial Y chromosome(s) could result from a normal Y gene that continues to function in the absence of normal testicular tissue. It could also be caused by a defective gene on the Y chromosome, or it might be secondary to tissue disorganization.

Dr. S. Ohno (Loma Linda, California) led a discussion about homologies between the testis and the ovary. Spermatogonia are homologous with oogonia, Sertoli cells with granulosa cells, and Leydig cells with thecal cells. He then described a species of fish whose gonads can change from ovary to testis during adulthood. There is always one male in the school of fish. If the male dies or disappears, the dominant female becomes the male for the school by differentiation of the ovary into a testis.

The HY antigen (HY Ag) was discussed by several symposium participants. Three assays for HY Ag exist: (1) transplant rejection, (2) cell mediated cytotoxicity, and (3) serological. The latter assay employs a male-specific polypeptide antigen, 18-20 D in size, that is present in body fluids and expressed in Sertoli and Leydig cells. Dr. Page tried to clarify the issues: HY Ag was initially defined as a transplantation-rejection antigen. T-cell assays recognize transplant Ag. There is no evidence that the serological Ag is

the same HY Ag that is identified by the other two assays. The conclusion was that the nomenclature regarding HY antigens is totally inadequate. The result is that we are often talking about different things when we discuss HY Ag.

Dr. C. Lau (University of California, San Francisco) extended the discussion, stating that the serological HY Ag in humans is a glycoprotein of 185 amino acids; it is found in both males and females. The gene is not localized on the Y chromosome but on chromosome 6. The HY Ag gene identified by the other two assays is located on the Y chromosome.

Dr. J.L. Simpson (Memphis, Tennessee) postulated that (1) the X and Y chromosomes are not solely responsible for gonadal differentiation; (2) X and Y determining factors are solely regulatory; (3) the structural loci for gonads are on autosomes; and (4) X and Y gonadal determining genes are identical and the different effects result because of a dosage effect produced by X inactivation in the female. The latter postulate would be theoretically possible and consistent, in part, with the concepts presented by Dr. Page. For example, the female would have half the gene dosage for TDF as the male since one X is inactivated.

Dr. Simpson reported that more than 12 45,XO patients have become pregnant. He emphasized that oocytes can develop in testicular tissue, and gonadal stroma may therefore play a role in gonadal differentiation, at least in cer-

tain instances. The existence of 46,XY individuals with female phenotype or ambiguity as part of the gonado-palato-cardiac syndrome supports this concept. The gonads in persons with this syndrome have been variously reported to be streaks, ovaries, and testes.

Primary amenorrhea resulting from deletions of the short arm and from small deletions of Xq 11.2-11.4 was also reported. Deletions at Xq 13 may be associated with secondary amenorrhea. A gene or genes in that region would appear to be associated with ovarian maintenance and thus prevent premature menopause. Individuals with deletions between or including Xq 21-25 have minimal abnormalities (although they are not necessarily normal) and frequently have secondary amenorrhea.

Dr. Judith Hall (University of British Columbia) said that many of the phenotypic defects observed in Turner syndrome may be secondary to intrauterine lymphedema and pressure phenomena resulting from this edema. Even coarctation of the aorta could be secondary to this phenomenon. She states that the dysmorphology in Noonan's syndrome might be related to intrauterine lymphedema. This concept, if true, would make it unproductive to look for specific genes responsible for each phenotypic feature.

The data presented during this session add greatly to our understanding of Turner syndrome.

## Special Report: The March of Dimes Clinical Genetics Conference— July 19-22, 1987, Minneapolis, Minnesota

Judith G. Hall, M.D.  
*Associate Editor*  
*Growth, Genetics, and Hormones*

The theme of this conference was "disorders of the neural crest and craniofacial skeleton." Thus, neural crest development and the possible effects of teratogens upon it were reviewed. Clearly, neural crest cells in the cranial area are more diversified in their

actions than neural crest cells in the trunk.

A number of new experimental techniques permit identification of neural crest cells and observation of their migratory patterns in experimental animals. In the craniofacial area, neural crest cells or ectomesenchymal tissue separate from the neural tube laterally and migrate within the mesoderm to form somitomeres, which are

segmental areas within the cranial region. The neural crest cells provide muscle and bone, as well as endothelial cells for angiogenesis, in the cranial area. In the trunk, neural crest cells play a role primarily in pigmentation and in development of the autonomic nervous system.

Utilization of a Nile blue stain to indicate areas of necrosis in an embryo permits the suggestion

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**The March of Dimes  
Clinical Genetics Conference  
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that there are large areas of cell death that are programmed as part of normal embryological development. These areas that are programmed for cell death seem to be accentuated by teratogens,

appearing earlier and resolving later than they normally would.

It was clear from the presentations that simple neurocristopathies, which are associated with single defects, should be distinguished from complex neurocristopathies, which are characterized by structural anomalies and/or ongoing problems, such as dysplasia and overgrowth.

A number of new craniofacial syndromes were described, but the classification of neural crest disorders is still very difficult and complex. New imaging techniques, such as magnetic resonance imaging and stereoradiophotogrammetry, are improving our abilities to diagnose and describe the natural history of already described conditions.

**Special Report: 26th Annual Meeting of the European Society for Pediatric Endocrinology (ESPE)—September 6-8, Toulouse, France**

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The presentations at the annual meeting of the ESPE reflect the broad spectrum of interests of ESPE members, who come from many countries, each with different administrative structures and facilities for clinical and basic research in pediatric endocrinology. The main topics of ESPE meetings are therefore aimed at reviewing current developments for a broader audience and at informing selected audiences about recent advances in endocrine research. This year's plenary lectures were devoted to pediatric aspects of endocrine autoimmunity, regulation of growth hormone (GH) secretion by growth-hormone-releasing hormone (GHRH) and somatotropin-release-inhibition hormone (SRIH), and the cDNA of the human insulin receptor and its potential pathologic expression.

Dr. H. A. Drexhage reviewed the more conventional disorders of endocrine autoimmunity. The primary purpose was to point out the contrasting effects of autoimmune reactions, which may stimulate endocrine tissues but may also lead to their destruction. The basic principles of these reactions and the methodologies used to evaluate them have been derived from investigations of disorders of the thyroid gland. Recently, however, a variety of other disorders that mimic classical endocrine disorders but also have an auto-

immunologic pathogenesis have been discovered. Examples are pigmented adrenocortical micronodular dysplasia (PAMD) and precocious puberty. Dr. Drexhage's reference to the high incidence of transplacental passage of thyroid-growth-blocking antibodies as a cause of thyroid agenesis (or ectopia)—a mechanism suggested many years ago by Dr. R. Blizzard—was also supported by a report of Grütters et al (Berlin, West Germany). These investigators found cytotoxic thyroid autoantibodies in 32% (12 of 37) of newborns with hypothyroidism. Dr. Drexhage left his audience with the impression that more advanced techniques to quantitate autoimmune processes would make this field one of the most important areas to investigate in endocrinology.

Dr. W. Wehrenberg summarized what is currently known about GH regulation by GHRH and SRIH. Numerous clinical and experimental investigations are under way in this area, and new data emerge almost daily. Although SRIH appears to play a dynamic role in controlling GH secretion, the pulsatility of GH secretion does not appear to be determined solely by SRIH. Because a multitude of factors influence GH secretion, the two prominent hypothalamic hormones obviously cannot explain all the phenomena of GH secretion that are observed in various clinical states. There are also indications that GHRH exerts a negative effect on GH secretion by reducing GHRH receptors at the

pituitary level. Dr. Wehrenberg also reported a remarkable finding from his work on prenatal growth control: Administration of GHRH antibody to pregnant rats results in smaller offspring.

Two sessions dealt with Cushing syndrome and neonatal hyperinsulinism. Since both disorders are relatively rare in childhood, clinical experience with children with these disorders is still limited. A multicenter approach to standardize modes of diagnosis and treatment was advocated for neonatal hyperinsulinism, a condition whose prognosis is essentially determined by effective prevention of hypoglycemic states. Dr. A. Aynsley-Green pointed out that glucose, diazoxide therapy, and surgery are still the most important modalities in the management of neonatal hyperinsulinism. Based on his experience in cases of disseminated  $\beta$ -cell hyperplasia, Dr. Aynsley-Green advocated a subtotal pancreatectomy (about 95%) to prevent recurrences, which are observed frequently after less radical surgery.

A major segment of the meeting focused on problems related to the potential of GH to improve growth in growth disorders other than "classical" GH deficiency (GHD). Rather than provide solutions to these problems, investigators presenting papers attempted to put the confusion regarding GH measurement into perspective. Several presentations were devoted to GH testing and measurement of spontaneous GH secretion. With respect to spontaneous

GH measurements, for example, there is a diversity of blood-sampling methods and wide variability in approaches to evaluation of the data obtained by these methods. The critical observer was left with the impression that standardization of GH measurements and other parameters

among investigators is badly needed to ensure consistency in reporting data. Similarly, trials evaluating treatment of different growth disorders with GH and GHRH need to be conducted with great care and more patients to validate results. Similar standardization problems appear to be

prevalent in various studies evaluating the treatment of precocious puberty with luteinizing-hormone-releasing-hormone analogues.

The next ESPE meeting will be held in Copenhagen in June, 1988. It will focus on the testis and endocrine problems associated with malignancies.

## Special Report: 8th Annual Workshop on Malformation and Morphogenesis— August 15-19, 1987, Greenville, South Carolina

Judith G. Hall, M.D.

Associate Editor

*Growth, Genetics, and Hormones*

Several reports on a variety of congenital defects and inherited syndromes in animals and humans were presented at this workshop. Dr. W. Webster (Sydney, Australia) reported that handling the uterus of the pregnant rat during surgery, or for nonsurgical reasons, can lead to limb defects and central nervous system damage compatible with vascular compromise. This may have clinical implications, although there is no evidence that the same sort of anomalies are seen with manipulation of the human uterus during pregnancy.

Dr. C. Stevens (University of Utah) described a carefully done study of the development of embryonic and fetal palmar and digital creases. Finger creases are well-defined by nine weeks and palmar creases by 12 weeks. These observations are important for timing various effects on limb development.

Dr. S. Clarren (University of Washington) described a carefully controlled experiment assessing "binge drinking" in monkeys. Large doses of alcohol (2.5-4.1 g/kg) given during the first week of pregnancy (and on a weekly basis thereafter) can have a significant impact on the fetal development of the monkey in terms of behavior and cognitive developmental delay measured after birth.

Dr. J. Cordero (Atlanta, Georgia) discussed research that suggested the use of multivitamins before conception may reduce the

risk for neural tube defects and possibly for other congenital anomalies.

Excellent studies by Dr. S. Cassidy (University of Connecticut) on Prader-Willi syndrome and Dr. C. Morris (Phoenix, Arizona) on Williams syndrome provided data that allow much better definition of the natural history of these conditions. The studies also suggest that many features thought to be part of the syndromes—such as obesity in Prader-Willi syndrome and behavior in Williams syndrome—can be modified. Long-term follow-up of patients with Weaver syndrome and Robinow syndrome was discussed by their namesakes.

Several reports suggested the possibility that many disorders with patchy areas of dysplasia (such as the McCune-Albright and Proteus syndromes) may represent somatic mosaicism due to single gene changes and chromosome changes.

Dr. K. Jones (University of California, San Diego) described research in which it was demon-

strated that the supraorbital ridge has a role in inducing the contour of the eyebrow. Individuals with aberrant supraorbital ridges will have aberrant placement of the eyebrows.

Dr. P. Duncan (Downstate Medical Center, Brooklyn, New York) presented an analysis of a family with three generations of Russell-Silver syndrome, a condition that is usually nonfamilial.

Reporting on Joubert syndrome, Dr. D. Flannery (Medical College of Georgia) showed a videotape that visually demonstrated the functional changes that occur in affected patients. These changes are sometimes hard to describe, but recognizing them is essential for an accurate diagnosis. The pattern of respiration in Joubert syndrome is quite striking, with episodic hyperpnea and abnormal eye movements. CAT scans of patients with these breathing and movement patterns may demonstrate the aplasia of the cerebellar vermis associated with Joubert syndrome.

### In Future Issues

Osteogenesis Imperfecta: An Update  
by Peter Byers, M.D.

### Lipodystrophy

by William L. Clarke, M.D.

### Medical Complications of the Skeletal Dysplasias

by Judith G. Hall, M.D. and  
David L. Rimoin, M.D., Ph.D.

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## Statural Development Parallels IGF-I Levels in Subjects of Constitutionally Variant Stature

Serum levels of insulin-like growth factor I (IGF-I) were estimated in 92 children with stature greater than 2 SD above normal for age (tall) and in 109 with stature less than 2 SD below normal for age (short). A protein-binding assay was used on acid gel-filtrate serum. In this assay, IGF-II has half the displacing capacity of IGF-I.

The level of IGF-I increases as age increases. However, for a given bone age (Greulich-Pyle), IGF-I levels are significantly higher in tall than in short children (over the bone age range 2 to 16 years). Also, for a given pubertal stage (Tanner), tall children have significantly higher IGF-I levels in P2, P3, and P4-5 (definition of P not given). At completion of growth, tall children had significantly higher IGF than short children.

The authors conclude that differences in the secretion rate of IGF-I may be associated with differences in stature.

Binoux M, Gourmelen M. *Acta Endocrinol* 1987;144:524.

**Editor's comment**—The question of whether tall people have greater

growth hormone secretion or IGF-I production than short people, or both, is unresolved. Although this article speaks in favor of the association between high IGF-I levels and tall stature, the degree of association is quite small. The most that can be said is that the difference in secretion rate (already a jump from serum level) is only a relatively minor factor among the perhaps multiple causes of tallness or shortness. At each stage of puberty, for example, there is overlap between the distributions, although there is also separation of the means. One of the authors' graphs shows that within neither the tall nor the short group is there a significant relationship between growth rate for age and IGF-I for age; only when these two extreme groups are pooled does a correlation emerge, which is therefore an overestimate of the true population value. It may be, of course, that larger people produce a little more IGF on average than smaller ones, but they do not clear it from the blood relatively faster. It is unclear how cartilage levels of IGF-I relate to blood levels. Even if we take this association between serum IGF and height at its face value, it is clear that the main cause of human stature differences resides elsewhere.

James M. Tanner, M.D., D.Sc.

## The Effect of Exercise on Plasma Somatomedin-C/Insulin-like Growth Factor-I Concentrations

Nutritional status is well known to be an important determinant of plasma somatomedin-C/insulin-like growth factor (Sm-C/IGF) levels, and reductions are observed in malnutrition and during prolonged fasting. Previous studies have suggested that both dietary protein and energy intake modulate Sm-C concentrations. The present study was undertaken to determine whether an energy deficit induced by vigorous exercise is associated with a reduction in Sm-C.

Six healthy, exercise-conditioned males were fed a constant diet and were exercised, and they expended 14.1-16.3 kcal/kg/day. Their plasma Sm-C concentrations declined significantly during the last two days of the seven-day exercise period.

After three days of reacclimation, the subjects had their calorie intakes reduced by the same number of calories that had previously been expended in the form of exercise. Once again, a fall in Sm-C concentrations was

## A Longitudinal Study of the Relationship of Plasma Somatomedin-C Concentration in the Pubertal Growth Spurt

Beginning at puberty, 12 boys and eight girls underwent yearly measurements of plasma somatomedin-C (Sm-C) levels. For each subject, age at peak height velocity (PHV) was determined and the Sm-C levels plotted in relation to years before and years after PHV. Not all subjects were followed for the entire study period: There were 19 subjects at PHV and PHV + 1

year, 15 at PHV-1, 16 at PHV + 2, 11 at PHV-2, and ten at PHV + 3. Sm-C levels were determined by radioimmunoassay (control adult value, 1.0 U/mL).

Sm-C levels rose sharply in parallel with the increase in height velocity, but the peak Sm-C level occurred one year after PHV, averaging 3.5 U/mL in both boys and girls. The minimum peak value was 1.5 U/mL. After the peak level occurred, the decline was very slow, and quite unlike the decline in height velocity. By PHV + 3 the Sm-C level still averaged about 2.8 U/mL. Therefore, plasma Sm-C

levels correlate with height velocity only in early puberty.

Cara JF, Rosenfield RL, Furlanetto RW. *Am J Dis Child* 1987;141:562.

**Editor's comment**—This paper is a good example of how the correct use of auxological methods enables the extraction of important conclusions from a small study. Although the use of years before and after PHV as a scale of developmental age was initiated in the 1930s, it is still far from universal.

The authors' result is striking: The Sm-C curve looks more like

noted, and the magnitude of this fall was not different from that observed during exercise. Nitrogen balance, measured daily throughout the studies, averaged  $-1.6 \pm 1.7$  g/day during the last three days of exercise but  $-3.5 \pm 1.73$  g/day during dietary restriction.

According to the authors, these results demonstrate that strenuous exercise produces a negative calorie balance and results in a fall in Sm-C concentrations equivalent to those seen in caloric restriction without exercise. However, exercise appears to have a nitrogen-sparing effect. This observed nitrogen-sparing effect with exercise could not be explained by the study design.

Smith AT, Clemons DR, Underwood LE, et al. *Metabolism* 1987; 36:533-537.

**Editor's comment**—This study suggests that children who exercise strenuously and limit their calorie intake may have reduced plasma Sm-C concentrations, which could lead to attenuation of linear growth. All care should be taken to make certain that children who are involved in strenuous athletic training have an adequate intake of nutrients.

William L. Clarke, M.D.

the testosterone curve than that of any growth variable. When does the Sm-C level eventually drop to the adult value? And why? The authors suggest that the high levels seen several years after PHV may reflect bone and muscle growth, which continues somewhat after PHV. By PHV+3, however, there is little additional lean body mass to come. Clearly, more extended longitudinal studies are needed before we can grasp the mysterious relationship between plasma Sm-C levels and growth rate.

James M. Tanner, M.D., D.Sc.

## Impaired Response of GHRH Measured in Plasma After L-Dopa Stimulation in Patients With Idiopathic Delayed Puberty

The advent of an assay to measure growth-hormone-releasing hormone (GHRH) permitted the authors of this report to compare GHRH and growth hormone (GH) levels in two groups of patients: 16 with idiopathic delayed puberty (IDP) or constitutional delay of growth, and 12 with what the authors call constitutional short stature, which is synonymous with genetic short stature. All patients were in stage 1 or early stage 2 of sexual development. The mean GH values after stimulation with L-Dopa were  $8.6 \pm 1.4$  ng/mL (SEM) in those with IDP and  $12.0 \pm 0.8$  ng/mL in those with genetic short stature. The difference was not statistically significant. The GHRH values were  $41.0 \pm 10$  pg/mL in the IDP subjects and  $96 \pm 25$  pg/mL in those with genetic short stature ( $P < 0.02$ ). Five patients with IDP and the most severe delay in growth velocity (more than 2 SD below the bone age growth

velocity) had a mean value of 17.3 pg/mL. Values were  $75.0 \pm 14.5$  pg/mL for those with normal growth velocity.

The authors state that these data suggest a hypothalamic dysfunction in patients with IDP.

Argente JD, Evans Brian D, Donnadiue M et al. *Acta Paediatr Scand* 1987;76:260.

**Editor's comment**—The conclusions of the authors are logical. Although the difference in GH values in the two groups was not statistically significant, a closer look at the range of GH values (presented in a graph) indicates that seven of the 16 patients with IDP had values lower than any of those obtained from the 12 patients with genetic short stature. These data would suggest that there is a decreased peak of GH secondary to L-Dopa stimulation in patients with IDP. Unfortunately, the authors do not correlate the GHRH and peak GH values for each patient, nor do they give or refer to data pertaining to total GH output following L-Dopa administration. Nevertheless, the data do support the concept presented.

Robert M. Blizzard, M.D.

## Knemometry in Assessment of Linear Growth

Four health care professionals, one an auxologist, the others doctors or nurses, measured 18 children aged 5.5 to 10.5 years every month between 5 PM and 8 PM for six months. Each child was measured sequentially and independently by two observers at each measuring session, during which single measurements of stature and sitting height and six measurements of lower leg length (LLL) were taken. Children were asked to walk a few steps between each of the LLL measurements. In a second series, four LLL measurements were made weekly for six weeks on six children.

The coefficients of variation of the six sets of measurements in the first series averaged 0.10%, with the highest being 0.25%. The coefficients of variation of the four sets of measurements in the second series had a highest value of 0.18%. Thus, four measurements, with the most aberrant deleted in determining the average, are as good as six, and are recommended in assessing linear growth.

Although there were significant intra-observer differences in LLL (due to differences in initial positioning of the child), there were no such differences in LLL increments. However, the stature measurements made by the auxologist were considerably more reliable than those made by the doctors

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### ***Knemometry In Assessment of Linear Growth***

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and nurses. When lines were fitted to the monthly stature values for each child, the SD of the points around the line was only half as large for the auxologist's measurements as for the measurements made by the others.

The velocities over the six months (obtained by linear fit for LLL and stature) correlated poorly, ranging from 0.32 in nine children measured by a doctor or nurse to 0.76 in 11 children measured by the auxologist. The agreement on these fitting velocities between observers was no better for LLL than for stature.

The values of growth velocity seen at six months were very badly predicted by values seen at one month, with the average deviation about the prediction being no less than 50%. Deviations in predictions from values seen at two and three months were about 25% and 17%, respectively. The deviations were nearly the same for LLL and stature.

In the second series, in which measurements were taken weekly, significant week-to-week variations in LLL velocity were seen. These variations were sometimes, but not always, associated with transient illness. Six children measured for three weeks before and three weeks after tonsillectomy had decreased LLL velocity for two weeks, followed by catch-up growth.

Wales JKH and Milner RDG. *Arch Dis Child* 1987;62:166.

***Editor's comment—***This is a very important paper on knemometry because the design is comprehensive and the results clear-cut. The authors summarize their conclusions by saying that velocities seen at six months cannot be usefully predicted by velocities measured at one, two, and even three months. LLL can be measured ac-

curately, as claimed by its originator, but LLL growth rates vary from month to month and week to week. Thus, the authors suggest that similar discrepancies in stature are due to inherent inaccuracy of the technique rather than to inherent variation. However, this does not necessarily follow from their results. If they are correct, then stature would definitely be a more accurate index for short-term prediction of longer-term measurements, for it has to be said that the physicians and nurses taking the measurements in these studies were not very accurate. Their maximum intra-observer difference of 1.6 cm can turn up occasionally, but their standard deviation of intra-observer differences averaged 0.5 cm, which means that

values approaching 1 cm were not that infrequent. We need to evaluate stature measurements as long-term predictors, but the measurements must be highly accurate and the design similar to that for LLL. My clinical impression (supported by an analysis of my data) is that the inherent variability of short-term velocities for stature, though perhaps less than LLL variability, precludes using one-, two-, and three-month rates as useful predictors for six-month or 12-month ones. Dr. Michael Hermannsen, who has had much experience with the knemometer, makes the same point in a letter [Arch Dis Child 1987;62:763] supporting the findings of Wales and Milner discussed here.

James M. Tanner, M.D., D.Sc.

### ***Fragile X Syndrome***

Fragile X syndrome is a common cause of mental retardation. Since it is almost always familial, recognition of the syndrome is important for the whole family. Affected boys tend to be large, with large heads and ears, and they are occasionally confused with patients who have Soto's syndrome. Typically, they have long faces and macroorchidism, although these features may not be present until after puberty. About 20% of patients have hyperextensible joints, mitral valve prolapse, and pectus excavatum.

A particularly distressing feature of the Fragile X syndrome is that a large number of males exhibit autistic behavior and many have repetitive hand movements. Hyperactivity may be present prior to puberty and can be very distracting. Cluttered speech, including a rapid rate of disfluency, stuttering, and perseveration, is typical.

About one third of girls who are carriers of the gene for Fragile X syndrome also manifest the syndrome's clinical features. Recent work suggests that about one in 1,500 males and one in 750 females carry the abnormal gene. About 4% of cases of severe men-

tal retardation among males can be attributed to Fragile X syndrome, although males may transmit the abnormal gene without being affected themselves.

Investigators working at the molecular genetic level have demonstrated a number of linked markers on the X chromosome. Therefore, prenatal diagnosis of the Fragile X syndrome may be possible with the aid of cytogenetic and linkage studies.

Chudley AE, Hagerman RJ: *J Pediatr* 1987;110:821.

***Editor's comment—***Because of its genetic implications, clinicians must be aware of this very important syndrome. A major effort is being made to isolate the gene, which would improve the accuracy of linkage studies and provide better understanding of the pathogenesis.

Judith G. Hall, M.D.

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"Restriction Fragment Length Polymorphism: Applications to Linkage Analysis"  
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## MEETING CALENDAR

**May 2-6** Annual Meeting of the American Pediatric Society/Society for Pediatric Research. Sheraton Hotel, Washington, DC. Contact: Debbie Wogenrich, Executive Director, Society for Pediatric Research, 2350 Alamo SE, Suite 106, Albuquerque, NM 87106 (505-764-9099)

**May 6** Annual Scientific Session, Lawson Wilkins Pediatric Endocrine Society. Sheraton Hotel, Washington, DC. Contact: Debbie Wogenrich, Executive Director, Society for Pediatric Research, 2350 Alamo SE, Suite 106, Albuquerque, NM 87106 (505-764-9099)

**May 9-13** Clinical Disorders of Bone and Mineral Metabolism. Detroit, Michigan. Sponsor: Henry Ford Bone and Joint Specialty Center. Contact: Henry Ford Hospital, Continuing Medical Education, 2799 West Grand Boulevard, Detroit, MI 48202 (800-662-8242, within Michigan; 800-521-7946, other states and international)

**June 8-10** 70th Annual Meeting of The Endocrine Society. New Orleans, Louisiana. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

**July 8-10** International Symposium on the Marfan Syndrome. Baltimore, Maryland. Contact: Diane Heydinger, Johns Hopkins University School of Medicine, 720 Rutland Road, Baltimore, MD 21205 (301-955-2959)

**July 10-13** 20th Anniversary of the Clinical Genetics Conference. Baltimore, Maryland. Contact: Carlita Kearney, Johns Hopkins University School of Medicine, 720 Rutland Road, Baltimore, MD 21205 (301-955-2959)

**July 20-23** 15th International Audiology Congress. Exeter University, Exeter, England. Contact: Prof. J.M. Tanner, Room 115, Institute of Child Health, 30 Guilford Street, London, England WC1N 1EH

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# GROWTH

## Genetics & Hormones

Vol. 4 No. 2

June 1988

## Osteogenesis Imperfecta: An Update

Peter H. Byers, M.D.

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*Center for Inherited Disease*

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*Seattle, Washington*

For most families, the birth of a child with osteogenesis imperfecta (OI) raises three questions: How will my child do? Will it happen again? Why my family?

The clinical, biochemical, and genetic approaches taken during the past several years to understanding OI are beginning to provide answers to these questions. We now know something about the natural history of each of the phenotypes observed with OI, and we know a little about the molecular basis and heterogeneity of the disease(s). Thus, we can predict (and prevent) recurrence, even though we understand relatively little about why it occurs.

Attempts to develop a classification of OI were made as soon as heterogeneity was recognized. The efforts had two goals: to determine the natural history of OI and to identify families at risk for recurrence. No classification has yet achieved these goals. Because of the dynamic nature of the disease, the occasionally marked intrafamilial variability, and evidence of recurrence due to germline mosaicism for dominant mutations, no classification system will succeed completely.

The classification that most successfully meets the goals, and is generally used by geneticists, was developed by Silence and his colleagues. *Four types of OI* were distinguished on the basis of clinical presentation, radiologic criteria, and mode of inheritance:

(1) OI type I, a dominantly inherited variety with blue sclerae, bone fragility, and normal or near normal stature;

(2) OI type II, a form that is lethal in the perinatal period and was thought to be inherited in an autosomal recessive fashion but is now known to result from new dominant mutations;

(3) OI type III, a severe, progressively deforming form first thought to be inherited in an autosomal recessive fashion but now recognized to be genetically heterozygous;

(4) OI type IV, a dominantly inherited form with normal sclerae, mild to moderate (but variable) short stature, and mild to moderate deformity. Additional clinical, biochemical, and molecular genetic studies have expanded and clarified the initial classification (Table).

To put the current biochemical and genetic approaches in appropriate perspective, one must understand the structure and synthesis of type I procollagen.

### Biosynthesis and Structure of Type I Procollagen

Type I procollagen, the precursor of type I collagen found in tissues, is a heterotrimer that contains two identical  $\text{pro}\alpha 1(I)$  chains and a single  $\text{pro}\alpha 2(I)$  chain. The genes that encode the two proteins are members of a multigene family (the collagens) and are located on chromosome 7 (where  $\text{COL1A2}$  encodes the  $\text{pro}\alpha 2(I)$  chain) and chromosome 17 (where  $\text{COL1A1}$  encodes the  $\text{pro}\alpha 1(I)$  chain). The genes are complex, contain more than 50 exons each, and are transcribed, spliced, and processed in the nucleus. The mature messenger RNA (mRNA) is transported to the rough endoplasmic reticulum and translated on membrane-bound ribosomes. Although each gene is present in a single copy, they are differentially transcribed so that the steady-state mRNA levels reflect the 2:1 chain ratio found in normal molecules.

The  $\text{pro}\alpha$  chains have several major domains (Figure), an amino terminal globular domain, a long triple-helical segment characterized by the repeating amino acid triplet sequence of  $(\text{Gly-X-Y})_{338}$ , and a globular carboxyl-terminal

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## Osteogenesis Imperfecta: An Update continued from page 1

extension. During chain elongation, most prolyl residues in the Y position (about 100 per chain) of the triple helix are hydroxylated, some lysyl residues are hydroxylated, the rare hydroxylysyl residue is glycosylated, and heterosaccharide is added to a single residue in the carboxyl-terminal propeptide extension.

Assembly of chains into molecules begins once chain synthesis is terminated through domains located in the carboxyl-terminal propeptide extension and triple helix propagates from the carboxyl-terminal end toward the amino terminus. Glycine in every third position is necessary for triple helix propagation and the structure is stabilized by interchain hydrogen bonds. Hydroxyproline is also important for thermal stability.

Post-translational modification of the triple-helical domain is terminated with the formation of a stable triple helix. The intact molecules are transported to the Golgi apparatus, packed into secretory vesicles that fuse with the cell membrane, and discharged into the extracellular space. Outside the cell, the amino-terminal and carboxyl-terminal propeptides are removed and collagen molecules self-assemble into fibrils that are stabilized by lysine-derived covalent cross links.

### Osteogenesis Imperfecta Type I

OI type I is characterized by blue sclerae, normal or near normal stature, and autosomal dominant inheritance. Early studies indicated that individuals with OI type I had less type I collagen (compared with type III collagen) in skin than did normals. Decreased production of type I procollagen by

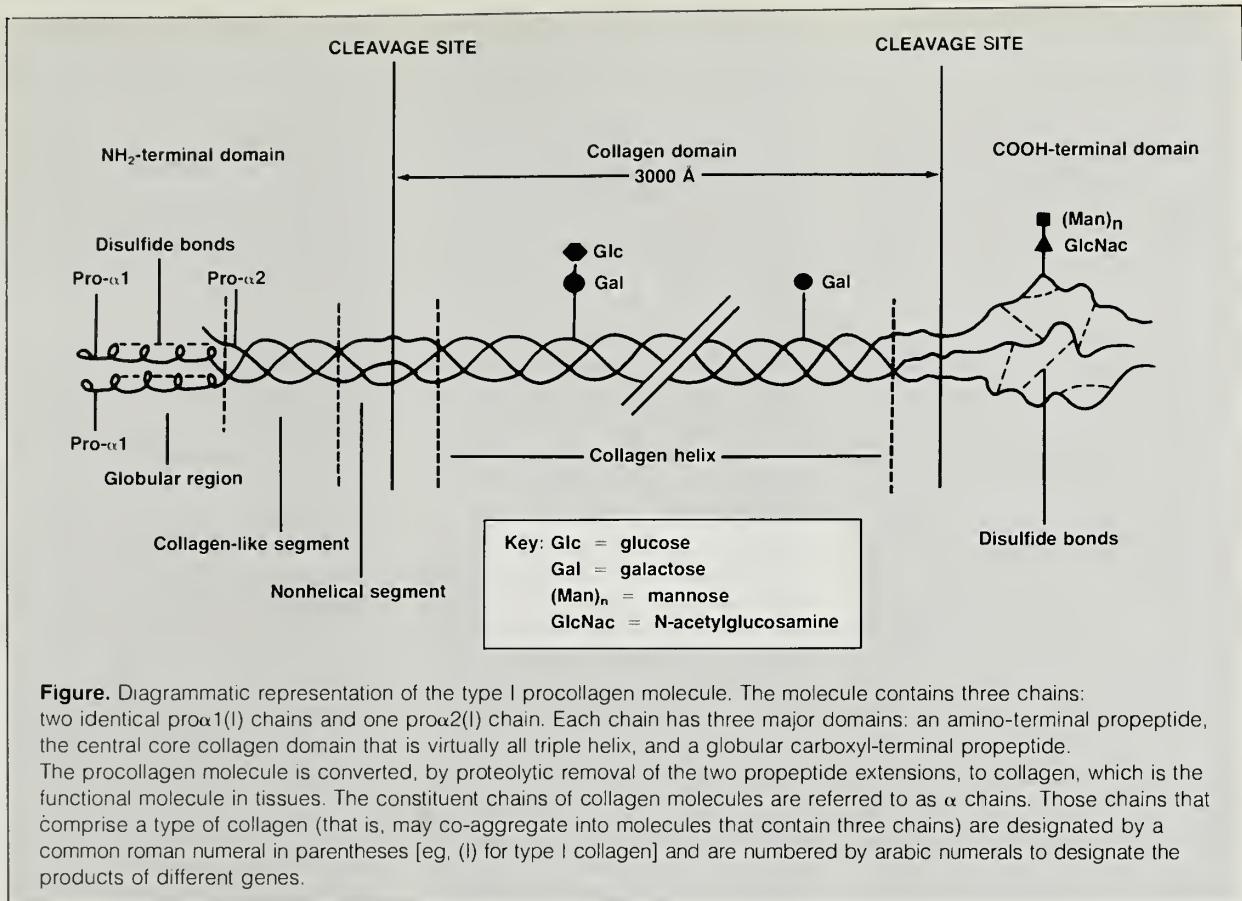
cells cultured from such patients results from synthesis of only half the normal amount of  $\text{pro}\alpha 1(\text{I})$ , which reflects the half normal levels of steady-state  $\text{pro}\alpha 1(\text{I})$  mRNA levels. Most individuals with the OI type I phenotype have mutations in one allele of the  $\text{COL1A1}$  gene.

Our analysis of the  $\text{COL1A1}$  genes from more than ten individuals with OI type I, and of the linkage data from more than twice that number of families, indicates that loss of the entire gene must be a rare event (no case has been identified yet). Instead, it appears that either the expression of the gene itself or its nuclear processing is disturbed. The decrease in production (and secretion) of type I procollagen occurs because stable molecules cannot be formed without two  $\text{pro}\alpha 1(\text{I})$  chains. Thus, when the number of  $\text{pro}\alpha 1(\text{I})$  chains is decreased to half normal, the amount of type I procollagen formed is also half normal and the

**Table.** Osteogenesis imperfecta: Clinical heterogeneity and biochemical defects

OI type	Clinical features	Inheritance pattern*	Biochemical defects
I	Normal stature, little or no deformity, blue sclerae, hearing loss in about 50% of individuals; dentinogenesis imperfecta is rare and may distinguish a subset	AD	Decreased production of type I procollagen
II	Lethal in the perinatal period, minimal calvarial mineralization, beaded ribs, compressed femurs, marked long bone deformity, platyspondyly	AD (new)	Rearrangements in the $\text{COL1A1}$ and $\text{COL1A2}$ genes Substitutions for glycyl residues in the triple-helical domain of the $\alpha 1(\text{I})$ chain
		AR (rare)	Small deletion in $\alpha 2(\text{I})$ on the background of a null allele
III	Progressive deformation of bones, usually with moderate deformity at birth; sclerae variable in hue, but often lighten with age; dentinogenesis common, hearing loss common; very short stature	AR	Frame-shift mutation that prevents incorporation of $\text{pro}\alpha 2(\text{I})$ into molecules Noncollagen defects
		AD	Point mutations in the $\alpha 1(\text{I})$ or $\alpha 2(\text{I})$ chain
IV	Normal sclerae, mild to moderate bone deformity, variable short stature; dentinogenesis is common and hearing loss occurs in some	AD	Point mutations in the $\alpha 2(\text{I})$ chain Rarely, point mutations in the $\alpha 1(\text{I})$ chain Small deletions in the $\alpha 2(\text{I})$ chain

\*AD = autosomal dominant; AR = autosomal recessive



**Figure.** Diagrammatic representation of the type I procollagen molecule. The molecule contains three chains: two identical  $\text{pro}\alpha 1(\text{I})$  chains and one  $\text{pro}\alpha 2(\text{I})$  chain. Each chain has three major domains: an amino-terminal propeptide, the central core collagen domain that is virtually all triple helix, and a globular carboxyl-terminal propeptide. The procollagen molecule is converted, by proteolytic removal of the two propeptide extensions, to collagen, which is the functional molecule in tissues. The constituent chains of collagen molecules are referred to as  $\alpha$  chains. Those chains that comprise a type of collagen (that is, may co-aggregate into molecules that contain three chains) are designated by a common roman numeral in parentheses [eg, (I) for type I collagen] and are numbered by arabic numerals to designate the products of different genes.

remaining  $\text{pro}\alpha 2(\text{I})$  chains are degraded. Linkage studies suggest that in some families the OI type I phenotype results from mutations in the COL1A2 gene, but better clinical descriptions are required to be sure that members of those families do not have OI type IV.

### Osteogenesis Imperfecta Type II

OI type II is generally lethal in the perinatal period. Radiographs of affected infants demonstrate a virtual absence of calvarial mineralization, beaded ribs, platyspondyly, and marked deformity of long bones with accordionlike compression of the femurs. Although OI type II was originally thought to be an autosomal recessive condition, recent clinical studies and the preponderance of biochemical and molecular genetic studies indicate that this phenotype usually results from heterozygosity for new dominant mutations in the genes that en-

code the chains of type I collagen.

OI type II is a biochemically heterogeneous disorder in which four classes of mutations have been recognized: (1) multiexon rearrangements (deletions or insertions) in the COL1A1 and COL1A2 genes, (2) point mutations in the COL1A1 gene, (3) short deletions from the COL1A1 gene, and (4) compound heterozygosity for mutations in the COL1A2 gene.

Three rearrangements have been characterized: (1) deletions of the triple-helical residues 327-411 in the  $\alpha 1(\text{I})$  chain, (2) deletion of triple-helical residues 586-765 in the  $\alpha 2(\text{I})$  chain, and (3) duplication of about 60 residues between triple-helical residues 123 and 200 in the  $\alpha 1(\text{I})$  chain. In each case, molecules that contain the mutant chains are poorly secreted and less stable than normal molecules.

Point mutations in five separate individuals have been characterized and each resulted in a substi-

tution for a glycyl residue within the triple-helical domain of the products of one COL1A1 allele (cysteine for glycine at 988, 904, or 748; aspartic acid for glycine at 883; and arginine for glycine at 391). The preponderance of cysteine-for-glycine substitutions reflects the ease of identification and characterization, *not* the relative frequency of the substitution. Only six of about 150 infants characterized have this mutation, slightly less than the predicted frequency. Cells from these infants produce two populations of type I procollagen molecules, some that are normal and others that contain the abnormal chains. The latter have undergone excessive post-translational modification of all chains (largely lysyl hydroxylation and hydroxylysyl glycosylation) from the site of the altered residue to the amino terminus of the triple helix.

The increased modification is  
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## Osteogenesis Imperfecta: An Update

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thought to reflect an alteration in the rate of triple helix propagation beyond the substitution or an alteration in triple helix integrity in that domain. Either alteration would allow continued modification. The "overmodified" molecules are delayed in their secretion, and the rate of intracellular degradation of abnormal molecules is increased. Assuming random association, a mutation in  $\text{pro}\alpha 1(\text{I})$  chains would affect 75% of all molecules produced so that 25% of the normal amount of collagen would be secreted. Depending on the stability of the abnormal molecules, variable amounts of the abnormal molecules would appear in the matrix. The abnormal molecules synthesized by cells that carry small deletions in the  $\text{pro}\alpha 1(\text{I})$  chains and by cells with compound heterozygosity for mutations in the  $\text{COL1A2}$  gene are unstable, poorly secreted, and degraded within the cells.

*How do these disparate mutations result in the same clinical and radiologic phenotype?* One unifying concept is that two factors are required to produce OI type II: a marked decrease in production of normal molecules, and the secretion of some type I collagen molecules in which the structure of the triple helix is disrupted. In this model, substitutions for a triple-helical glycine in the  $\alpha 1(\text{I})$  chain would disrupt winding and result in an unstable molecule that was overmodified from the site of substitution to the amino terminus and was poorly secreted. Overmodification probably affects the incorporation of abnormal molecules into fibrils and alters the interactions of these molecules with other matrix macromolecules. The rearrangements and small deletions similarly derange structure and appear to interfere with normal modification, stability, and secretion.

Although in most instances OI type II results from new dominant

mutations, there is an empiric recurrence rate of about 6%. Recurrence usually results from germline mosaicism for a mutation in one of the genes that encodes a chain of type I procollagen. In rare families, OI type II may be inherited in an autosomal recessive fashion. Prenatal diagnosis by ultrasound examination at about 15 weeks' gestation is reliable and analysis of collagen synthesized by cells from chorionic villi biopsied at ten weeks' gestation can provide diagnostic information.

### Osteogenesis Imperfecta Type III

OI type III is characterized by markedly short stature and progressive bone deformity during childhood and adolescence. The sclerae may be blue in infancy but are usually only pale blue or normal in adulthood. Dentinogenesis imperfecta is seen in some and hearing loss occurs frequently. Individuals with OI type III sustain multiple fractures. They often develop severe scoliosis that is difficult to treat, ultimately leading to cardiorespiratory compromise. OI type III was originally designated as an autosomal recessive condition, but it is now apparent that the phenotype is genetically heterogeneous, and both autosomal recessive and autosomal dominant varieties are known. The recessively inherited OI type III is probably rare except in certain populations, such as South African blacks, among whom it may be the most common form of OI.

With a small number of important exceptions, OI type III has been difficult to characterize biochemically. Among infants with recessively inherited forms, one child whose cells secreted type I procollagen that contained only  $\text{pro}\alpha 1(\text{I})$  chains has been identified. The child, a product of a consanguineous mating, was homozygous for a four base-pair deletion near the end of the coding region in the  $\text{COL1A2}$  gene; the frame-shift resulted in a short extension of the carboxyl-terminal propeptide. The change in sequence prevented the assembly of those  $\text{pro}\alpha 2(\text{I})$

chains into type I procollagen molecules. Both asymptomatic parents were heterozygous for the mutant allele.

In other families in which a single child is affected, and in some families in which a parent and a child are affected because of autosomal dominant inheritance, point mutations in  $\text{COL1A1}$  or  $\text{COL1A2}$  that affect triple helix stability have been identified. For example, a new mutation that results in a substitution of cysteine for glycine at position 526 of the triple helix in about half the  $\text{pro}\alpha 1(\text{I})$  chains synthesized has been identified in one infant. The *de novo* appearance of cysteine in  $\text{pro}\alpha 2(\text{I})$  between residues 6 and 327 (from which it is normally excluded) was identified in another infant. Thus, the dominant OI type III phenotype may overlap at the biochemical level with OI type II (point mutations in the  $\text{COL1A1}$  gene) and with OI type IV (see below). The phenotypic effect of a specific point mutation probably depends on the nature of the substituting residue and its location in the chain.

### Osteogenesis Imperfecta Type IV

OI type IV is a dominantly inherited disorder characterized by normal or greyish sclerae and normal to moderately short stature with significant deformity. Affected children are often born with femoral bowing that straightens with time and ambulation. Dentinogenesis imperfecta is common. Linkage studies have implicated mutations in the  $\text{COL1A2}$  gene as the cause of the OI type IV phenotype in several families. In one such family, substitution for the last glycine in the triple helix of  $\alpha 2(\text{I})$  (residue 1012 of the triple helix) results in OI type IV. Molecules that incorporate the abnormal  $\text{pro}\alpha 2(\text{I})$  chain are overmodified along the entire length of the triple helix and are secreted less efficiently than those that incorporate the normal chains.

Other mutations that result in small deletions or point mutations in about half the  $\text{pro}\alpha 2(\text{I})$  chains are responsible for the phenotype in most individuals with OI type IV.

These mutations all result in secretion of some molecules that have undergone excessive post-translational modification, and it is often difficult to distinguish between OI type II and OI type IV at the biochemical level. In OI type IV the mutations are usually in the COL1A2 gene and, as a result, only half the type I procollagen molecules are abnormal (compared with three quarters when mutations affect COL1A1 in OI type II). This quantitative difference may account for the milder disease phenotype in OI type IV.

### Other Forms of Osteogenesis Imperfecta

Not all individuals with OI readily fit the classic types. For example, one family has a phenotypic mixture of OI type IV and Ehlers-Danlos type VII features, probably explained by a short deletion from the pro $\alpha$ 2(I) chain near the amino-terminal end of the triple helix that interferes with the proteolytic conversion of procollagen and alters the bone matrix to produce bone fragility. As more families are studied, it is likely that similar "overlap" syndromes will emerge.

### A Unifying Picture

How do different mutations produce similar phenotypes, and why do similar mutations often result in markedly different phenotypes? While we do not have a clear answer to either of these questions, some integrating concepts are emerging. First, multixon rearrangements are lethal if they are expressed in proteins. Second, the effect of point mutations depends on the chain in which they occur, the residue substituted (glycine versus an X- or Y- position residue), the position in the chain, and the nature of the substitution. Third, there is a polar effect in the  $\alpha$ 1(I) chain such that point mutations in the carboxyl-terminal end of the triple helix (substitutions for glycine) are lethal while those toward the amino-terminal end may not be. Fourth, point mutations or small deletions in the  $\alpha$ 2(I) chain are generally milder in their phenotypic effects than those in the  $\alpha$ 1(I)

chain. Fifth, the phenotypic effect is a consequence of the presence of normal and abnormal collagens in the matrix and interaction among these molecules and the other components of the bone matrix. Finally, interfamilial heterogeneity is generally explained by different mutations while intrafamilial variation is likely to result from genetic differences in the expression or structure of other matrix components.

### Implications for Management and Treatment

The majority of individuals with OI have dominantly inherited disorders, either as a result of new dominant mutations or inheritance of the condition from a parent. Autosomal recessive phenotypes are rare. The distinction between the two can often be made from analysis of collagens synthesized by fibroblastic cells cultured from affected individuals. Biochemical analysis helps to distinguish among the types of OI. This, in turn, often allows for more appropriate counseling about natural history and facilitates prenatal diagnosis either by linkage analysis in families or analysis of collagens synthesized by chorionic villus cells. It should be stressed that intrafamilial variability can be marked and that our understanding of the correlation between the nature and location of the mutations and their phenotypic consequences is not yet complete.

Fractures can be treated by standard orthopedic measures. Disabling bone deformity can be corrected orthopedically to restore anatomic limb position and function, but early intervention is recommended. Surgery to correct major spinal deformities produces limited therapeutic results in the most severely affected individuals because of the compliant nature of the defective bone. Many medical treatments have been advocated through the years but their effectiveness is, at best, controversial. The variable responses to treatment that have been reported to date may reflect the biochemical heterogeneity of the condition. For

example, treatments designed to increase collagen production may be effective if the only effect of the primary mutation is to decrease production of normal collagen (eg, OI type I). These same treatments may be of little benefit if the OI phenotype results from incorporation of abnormal collagen into the matrix.

The immediate future holds immense promise for understanding the nature of mutations that result in the OI phenotypes. Only slightly beyond is the prospect of rational medical therapies that may emerge from understanding the molecular defects that produce the several forms of OI.

### References and Additional Readings

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# Medical Complications of Dwarfing Syndromes

Judith G. Hall, M.D.

*Associate Editor*

*Growth, Genetics, and Hormones*

David L. Rimoin, M.D., Ph.D.

*Associate Editor*

*Growth, Genetics, and Hormones*

Major progress in delineating the many specific skeletal dysplasias that present with disproportionate short stature has been made in the last 15 years. Each dysplasia has its own natural history, genetic basis, and specific pathological findings. However, some general comments can be made about the most common medical complications seen in children with these dwarfing conditions since they are of importance to the practitioner caring for these children.<sup>1-4</sup> These have been grouped into intrauterine, respiratory, central nervous system (CNS), skeletal, muscular, otolaryngologic, ophthalmologic, dental, and nutritional complications (Table).

## Intrauterine Complications

The most common problems seen during gestation are polyhydramnios and edema. In general, these occur in fetuses with the lethal chondrodytrophies, such as achondrogenesis and thanatophoric dysplasia. Occasionally, however, polyhydramnios is a late gestational complication in an otherwise nonlethal condition, such as achondroplasia.

Prenatal diagnosis of the chondrodysplasias by midgestational ultrasound is possible in many such conditions since normal measurements of limbs and trunk are available for comparison. When ultrasound is done because polyhydramnios is present, disproportionate fetal development may be noted. Observing the rate of growth over several weeks is often helpful in establishing a diagnosis. Prenatal diagnosis by ul-

trasound depends on whether the particular chondrodysplasia manifests itself before birth. Diagnosis of a specific chondrodysplasia during the second trimester permits two options: termination of the pregnancy or preparation of the family for the birth of a dwarfed child.

## Respiratory Complications

Respiratory distress is seen in a number of dwarfing conditions,<sup>5</sup> particularly those associated with small chests, such as asphyxiating thoracic dysplasia. Respiratory distress occurs when there is a small chest and lungs, a small or collapsing trachea, or a small upper airway; distress is worsened by respiratory tract infections. Norms for evaluating the size of the respiratory tree in children with chondrodysplasias are not readily

available. Respiratory rates and retractions are often the best indication that there is a problem. Monitoring oxygen and carbon dioxide levels is important in order to determine whether true respiratory distress exists in dwarfed infants.<sup>6</sup>

As the child grows, there is often a disproportionate increase in the size of the chest. During the first six months of life, the trachea in children with chondrodysplasias increases in size. During the second year of life, upper airway obstruction becomes a more significant problem than lower airway obstruction, particularly if the tonsils and adenoids are enlarged. Snoring and sweating during sleep are frequently seen in dwarfed infants. If persistent, these symptoms indicate that the child is having hypoxic episodes during sleep and requires further evaluation.

**Table.** Medical Complications of Dwarfing Syndromes

Intrauterine	Polyhydramnios; edema
Respiratory	Respiratory distress secondary to small chest and lungs, small or collapsing trachea, or small upper airway (often complicated by upper respiratory infections); asphyxiating thoracic dysplasia; snoring; upper airway obstruction; hypoxic episodes
Central nervous system	Hydrocephaly; spinal cord compression; nerve damage secondary to instability of cervical vertebrae
Skeletal	Kyphosis; instability of cervical vertebrae; various vertebral abnormalities; hip dysplasia; tight and loose joints; osteoarthritis; bowed legs; fractures
Muscular	Truncal hypotonia; disease of muscles; muscle contractures
Otolaryngologic	Frequent otitis media; hearing loss (conductive and neurosensory)
Dental	Malocclusions; dental crowding; structural abnormalities of teeth
Ophthalmologic	Severe myopia; retinal detachment
Nutritional	Obesity

## Central Nervous System

### Complications

#### Hydrocephaly

True hydrocephaly occurs in several dwarfing conditions, notably the achondroplasias, the metatropic dysplasias, and conditions that affect the base of the skull, and results in a decrease in the size of the foramen magnum and jugular foramen. Hydrocephaly can occur prior to delivery and, if the head is sufficiently enlarged, may lead to cephalopelvic disproportion and a traumatic birth. An infant with true hydrocephaly must be distinguished from one who has apparent hydrocephaly: ie, one with a normal-sized head and a small body.

In general, hydrocephaly, if present at birth or developing shortly afterwards, progresses during the first year of life. If disproportionate head growth occurs, a neurologic evaluation is essential. During the first year of life, serial ultrasounds through the fontanelle every three months give an indication of relative ventricular size. In the past, shunting operations were not performed unless the increase in head size was judged to be abnormal when compared with the growth charts of head circumference. However, there is increasing evidence that shunting should be considered in certain children with neurologic symptoms even if the head size remains stable, since increased intracranial pressure may be present and lead to CNS damage.<sup>7</sup>

#### Spinal Cord and Nerve

#### Damage

Compression of the spinal cord is seen at a number of vertebral levels in many of the chondrodysplasias. If the foramen magnum is small, compression may occur during the birth process. Instability of the cervical vertebrae can occur at this time when there is odontoid and vertebral or ligamentous laxity. The latter is seen in mucopolysaccharidoses conditions or when vertebral abnormalities are present, such as those associated with the spondyloepiphyseal dys-

plasias and spondyloepiphyseal dysplasias. Laxity of the ligaments is also seen in diastrophic dysplasia, metatropic dysplasia, Larsen syndrome, and camptomelic dysplasia.<sup>8</sup>

Instability of the cervical vertebrae can best be evaluated by lateral views of the neck during flexion and extension. If stability and subluxation are present, further evaluation by imaging and electrophysiologic techniques is indicated. The results may indicate the need for cervical fusion to prevent possible compression and quadriplegia. Sudden infant death, which has been reported with increased frequency in older infants with achondroplasia,<sup>9</sup> may be a function of high cervical cord compression. Occasionally, procedures to enlarge the foramen magnum must be considered.<sup>6</sup>

In conditions characterized by either vertebral abnormalities or short pedicles, or in disorders in which spinal abnormalities ultimately develop, spinal cord compression can occur at any time during life. In achondroplasia, symptoms of lower spinal cord and root compression usually do not occur until patients reach their early 20s. Symptoms of claudication and numbness must be taken seriously in patients with achondroplasia and should be treated medically by traction or bracing. If no relief occurs, surgical treatment is necessary in order to avoid permanent damage to the spinal cord and/or nerves.

#### Skeletal and Muscular

#### Complications

#### Hypotonia and Kyphosis

Patients with truncal hypotonia, which occurs in infants with achondroplasia or mucopolysaccharidoses, may develop kyphosis at the first or second lumbar vertebra. Kyphosis may be a function of weight distribution leading to compression of the anterior part of the vertebra. It may be possible to avoid this by positioning the baby properly so that increased weight is not placed on the anterior part of the first lumbar vertebra. Therefore, during the first year of

life or until good trunk strength develops, forward slumping of the body (eg, curling into the fetal position) should be corrected by repositioning the baby.

#### Hip Joint Abnormalities

Hip dysplasia is common in a variety of chondrodysplasias because the pelvis acetabulum is slow to form, the femoral head may be dysplastic (poorly ossified), or the femoral neck is short. In addition, the full range of motion of the hip joint is frequently limited by bony abnormalities. It is important that attention be given to proper acetabular formation during the first year of life; frog-leg positioning may be necessary to encourage good hip joint development. Severe osteoarthritis frequently occurs at the hip joint in children with epiphyseal and spondyloepiphyseal dysplasias, and early total hip replacement is required.

#### Bowed Legs

Bowing of the legs is frequent in many dwarfing conditions because the long bones of the leg grow disproportionately and the ligaments of the knee and ankle are relatively loose. In achondroplasia, the fibula overgrows and pushes the ankle inward. It is important to try to maintain normal distribution of weight on the joints of the leg to avoid asymmetric growth and wear and tear of the joint surfaces, since this produces osteoarthritis at a later time.

#### Fractures

Individuals with chondrodysplasias may have a higher incidence of bone fractures because of falls or trauma. Except in osteogenesis imperfecta, chondrodysplastic bones are generally of normal strength. In all dwarfing conditions, bone-healing rates seem to be normal.

#### Joint Stability

In certain dwarfing conditions, joint instability occurs because some joints are loose while others are tight. Loose joints lead to dislocation and excessive wear and

*continued on page 8*

## Medical Complications of Dwarfing Syndromes

*continued from page 7*

tear on the outer joint edges. Tight joints may be caused by bony limitation, such as the bony fusions that are seen in diastrophic dysplasia, or to disuse and contractures of the muscles in other dwarfing conditions. It is important to determine the cause of the tight joint in order to initiate appropriate therapy. In diastrophic dysplasia, where there is bony fusion causing tight joints, physical therapy would be inappropriate. However, in Kniest syndrome, where muscular atrophy frequently results from disuse of muscles, physical therapy is very helpful in maintaining range of motion and strength.

### **Arthritis**

Osteoarthritis (degenerative wear-and-tear arthritis) is a frequent complication of the chondrodysplasias. In many of the epiphyseal dysplasias, delayed ossification of a normal-sized epiphysis may lead to excessive wear and tear of the articular cartilage. Premature arthritis frequently develops in the weight-bearing joints of children with various chondrodysplasias. The activities of childhood and daily living should therefore be approached in a manner that minimizes excessive trauma and overuse of joints. Contact sports, which cause repeated wear and tear on the joints, should be avoided in children with conditions that correlate strongly with the development of arthritis.

### **Hearing and Speech**

Otitis media is a frequent complication of several skeletal dysplasias (eg, achondroplasia, spondyloepiphyseal dysplasia congenita, and Kniest dysplasia) in childhood. Aggressive antibiotic treatment is needed to avoid scarring of the eardrum and middle ear structures and to ensure that the child's hearing is normal so that he or she can develop normal social skills. There is some evidence that neurosensory loss develops if

chronic conductive loss occurs during childhood. Some conditions, such as osteogenesis imperfecta and diastrophic dysplasia, are associated with anomalies of the ossicles that lead to deafness. Since there is an increased incidence of hearing problems and otitis in most of the chondrodysplasias, hearing should be tested on a regular basis, particularly after upper respiratory infections.

### **Dental Crowding**

Many chondrodysplasias are associated with dental malocclusions or crowding because of overgrowth or undergrowth of the mandible or maxilla and because of structural abnormalities of the teeth. Regular dental check-ups are necessary, as is appropriate planning for orthodontic correction.

### **Ophthalmologic Complications**

Severe myopia and retinal detachments are seen in several spondyloepiphyseal dysplasias and in Kniest dysplasia. In children with these conditions, careful monitoring of vision is essential. Prophylactic laser treatment of the retina may be required to avoid retinal detachment.

### **Anesthesia**

Anesthesia can be a problem for individuals with some chondrodysplasias. Since frequent orthopedic surgical procedures are required, special care should be taken before and during the administration of anesthesia. The dosage of the anesthetic should be adjusted for the patient's weight. The possibility that the patient has unstable cervical vertebrae should also be kept in mind when the head is manipulated for intubation. Prior to the induction of anesthesia, flexion and extension of the cervical spine should be evaluated by lateral radiographs. Magnetic resonance imaging may also be necessary to evaluate flexion. Because the patient's trachea may be small, tracheal cuffs in several sizes should be available

in the operating room. Tracheal swelling can occur after extubation in diastrophic dysplasia. Some chondrodysplasias, such as osteogenesis imperfecta, seem to be associated with an increased incidence of malignant hyperthermia.

### **Obesity**

Obesity is often a problem in individuals with disproportionate short stature, particularly those with achondroplasia. The origin of obesity in achondroplasia is not clear, but it does not appear to be entirely due to psychosocial maladjustment. Because of the social ramifications of obesity and because of its significant contribution to increased wear and tear on joints, it is important for dwarfed individuals to try to maintain a normal weight. It is often hard to establish what the "normal" weight should be since there are no standard charts for weight in relation to disproportionate short stature. The best indicators of extra weight are general body appearance and the "pinch" test, in which the skin of the underarm or abdomen is pinched and the skinfold measured. If it measures more than 1 cm, the individual is probably overweight.

### **Obstetric and Gynecologic Care**

A number of obstetric and gynecologic problems are common in women with disproportionate short stature. Pregnant women will require a cesarean section for delivery because of a contracted pelvis. In women with achondroplasia, general anesthesia should be used for the cesarean section because of bony abnormalities of the spine. In addition, women with some types of disproportionate short stature reportedly have an increased incidence of fibroid tumors.

Sexual intercourse may be difficult for some women with dwarfing conditions because of the abnormal tilt of the pelvis. Because many of these women have short arms, personal hygiene can also be a problem. Both of these complications need to be discussed openly

with the woman and her partner, and practical solutions that are appropriate for them should be suggested.<sup>10</sup>

## Summary

The medical complications of chondrodysplasias are significant and require appropriate management. Therefore, physicians must be aware of these and other potential complications. Although visceral disorders such as congenital heart disease and renal anomalies are sometimes seen in patients with certain chondrodystrophies, they are generally not problematic.

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## In Future Issues

Lipodystrophy  
by William L. Clarke, M.D.

The Genetics of Various Forms of Rickets  
by Nadia Sakati, M.D.

Renal Disease and Growth Retardation: Physiology and Pathophysiology  
by David Powell, M.D., Ph.D.

Anabolic Steroids in Athletes: Efficacy or Fantasy?  
by Alan D. Rogol, M.D., Ph.D.

## Abstracts From the Literature

### Serum Concentrations of IGF-I, IGF-II, and Unsaturated Somatomedin Carrier Proteins in Children With Chronic Renal Failure

Growth failure in children with renal disease has multiple causes, including renal rickets, metabolic acidosis, chronic infection, and malnutrition. However, in some instances, chronic growth failure cannot be attributed to any of these causes. Because insulin-like growth factor (IGF)-I levels are often low in children with growth failure and renal disease, Powell et al examined the possible role of IGF-I, IGF-II, and their binding proteins.

Serum samples from 16 patients with glomerular filtration rates <50% of normal, who were on chronic peritoneal dialysis but did not have acidosis, rickets, or chronic infection, were compared with serum samples from normals. Acid chromatography permitted measurement of the actual amounts of IGF-I, IGF-II, and somatomedin carrier proteins (SmCP). The results revealed no diminution of the IGF levels, and an increase in SmCP.

On the basis of these data, di-

	Patients	Normals	P<0.05
IGF-I (ng/mL)	220 ± 182	248 ± 155	Not significant
IGF-II (ng/mL)	661 ± 213	433 ± 139	Not significant
SmCP (% IGF-I bound)	17% ± 3%	12% ± 3%	Significant

minished absolute values of IGF-I or IGF-II in serum cannot be the cause of the observed growth retardation. The authors suggest that the possible role of increased SmCP needs investigation.

Powell DR, Rosenfeld RG, Sperry JB, et al. *Am J Kidney Dis* 1987; 10:287-292.

**Editor's comment**—These findings both clarify and confuse the issue of the etiologies of growth retardation in chronic renal dis-

ease. Low serum IGF-I and IGF-II values in patients with chronic uremia, as tested by bioassay, radioimmunoassay, and radio-receptor assay, were repeated. Powell et al have demonstrated that there are inhibitors of the assay systems that can be removed by acid chromatography. The confusion arises because the cause of growth retardation remains obscure in many children with chronic renal disease who are not acidotic.

Robert M. Blizzard, M.D.

### Editor's Note

In the special report on the International Growth Hormone Symposium (Volume 3, Number 4), the second paragraph read as follows: "Drs. Gloria Tannenbaum and Joseph Martin demonstrated very convincingly that GH-releasing hormone (GHRH) is secreted in the posterior part of the hypothalamus (tubero-infundibular region) and that growth hormone-releasing factor (GRF) is secreted in the ventromedial and arcuate nuclei." While the statement is technically correct, the use of both GHRH and GRF in the same sentence may be misleading, since the terms are synonymous. The editor extends his apologies for any confusion this may have caused.

## The Measurement of Stature: Letter to the Editor

Recently Genentech, Inc. and Ross Laboratories distributed to many pediatricians a plastic instrument for the measurement of "standing" stature. This instrument consists of a vertical track (graduated in 1.0-mm and 0.16-inch increments), a movable horizontal headboard to be placed on the individual's head for measurement, and a track for the headboard, which is fixed to a wall to provide a flat vertical surface against which the heels, buttocks, scapulae, and head can be aligned. Installation is easy, and a bubble level is provided to ensure that the headboard is horizontal.

Dr. Alex Roche and colleagues conducted a small study of 30 children in which they compared the reliability of the apparatus with that of the Holtrain stadiometer and the Healthometer instrument, which is a scale for weight as well as a measuring device. In a Letter to the Editor, they reported that the Accustat stadiometer, distributed by Ross Laboratories and Genentech, Inc., is more reliable than the Healthometer and can be recommended as an alternative to the more expensive Holtrain stadiometer.

Roche AF, Guo S, Baumgartner RN, Falls RA. *Am J Clin Nutr* 1988; 47:922.

**Editor's comment**—The companies are to be commended for providing this device at no charge. Several members of the Editorial Board of Growth, Genetics, and Hormones have found that the data derived from its use are reproducible, as did Roche *et al.* Readers who would like to acquire the device for their use in the office or clinic are encouraged to contact their local Ross Laboratories representatives.

Robert M. Blizzard, M.D.

## Altered $G_s$ and Adenylate Cyclase Activity in hGH-Secreting Pituitary Adenomas

Three investigators from Milan report two groups of human growth hormone (hGH)-secreting adenomas. The groups are differentiated by the adenylate cyclase activity in the cells grown in culture and the amount of hGH released in the basal, stimulated, and inhibited states.

The results in Group 1 are similar to those observed in normal rat pituitary cells. The results in Group 2 were completely different. The stimulatory effect of magnesium in Group 1 was significant but was even greater in Group 2. This hyperresponse, which occurred only with magnesium stimulation, could account for the high cyclic adenosine monophosphate (cAMP) levels observed in cultured cells because it was already appreciated at physiologic magnesium concentrations.

The authors noted that the altered regulation of adenylate

cyclase in tumors in Group 2 concerned only the guanine-stimulatory ( $G_s$ ) mechanism and not the guanine-inhibitory ( $G_i$ ) mechanism on cAMP activity. The authors postulate that tumors in Group 2 probably have a disturbance of stimulatory transmembrane signalling, which is located in the  $G_s$  protein, while adenylate cyclase activity and its resulting function (hGH release) resides in the  $G_s$  but not the  $G_i$  protein.

Since both secretion and growth of pituitary somatotropes are known to be under the control of cAMP, the authors suggest that a direct causal relationship between the alteration of guanine and the high secretory rate of these cells and their growth is possible.

Vallar L, Spada A, Giannattasio G. *Nature* 1987;330:566-568.

**Editor's comment**—Professor Henry R. Bourne, of the University of California at San Francisco, addressed this subject in the same issue of *Nature*. In his commentary

## Risk of Hypoglycemia With Alternate-Day Growth Hormone Injections

This paper describes three children with growth hormone deficiency (GHD) who presented with fasting hypoglycemia 36-60 hours after an injection of growth hormone (GH). Each child was receiving thrice-weekly injections of synthetic GH; hypoglycemia no longer occurred once injections were begun on a daily basis.

The first patient was a 5-year-old boy with isolated GHD. He was placed on therapy with non-methionyl GH (Eli Lilly, Indianapolis), 60  $\mu$ g/kg IM, three days a week. This child began to experience nightmares 36-60 hours after GH injection, and his plasma glu-

cose values fell below 2.2 mmol/L. Simultaneous insulin-like growth factor-I (IGF-I) levels (measured by Nichols Institute) were 350-500 U/L, compared with 230 U/L prior to the initiation of therapy. Once daily injections of 30  $\mu$ g/kg IM were instituted, overnight plasma glucose levels rose and remained above 4.7 mmol/L.

The second child, a male with panhypopituitarism diagnosed at birth, was initially treated with thyroxine and cortisol. This resulted in complete resolution of hypoglycemia. When he was 20 months old, he was placed on therapy with methionyl GH (Genentech Inc, San Francisco) for growth failure and received 50 mg/kg subcutaneously three times a week. His blood glucose concentrations

	Group 1	Group 2
hGH secretion/30 min/2 x 10 <sup>5</sup> cells	53.1 ± 12.6 ng	246.7 ± 78.3 ng
With GHRH	132 ± 0.0 ng	no increase
cAMP levels	2.2 ± 0.1 pmoles	49.5 ± 18.7 pmoles
With GHRH	17.6 ± 0.0 pmoles	no increase
Adenylate cyclase activity	12.64 ± 1.51*	102.49 ± 23.2*
With GHRH	40.60 ± 3.59*	125.38 ± 29.64*
With GTP	26.30 ± 5.25*	92.14 ± 14.71*
With Gpp(NH)p	21.45 ± 3.58*	67.17 ± 11.08*
With NAF	127.09 ± 16.94*	94.90 ± 15.74*
With Forskolin	55.61 ± 10.68*	263.53 ± 30.71*
With SRIF	10.53 ± 2.22*	68.96 ± 7.52*

\*pmol cAMP mg<sup>-1</sup> protein min<sup>-1</sup>

("G Proteins and cAMP: Discovery of a new oncogene in pituitary tumors?"). Bourne presented two possible explanations for the autonomous function of the tumors in Group 2. These are either a covalent modification or an activating mutation of  $G_s$ . Bourne favors the

latter. He postulates that a somatic mutation in Group 2 tumors activates  $G_s$  directly and cites precedent for a mutational replacement of residues in the nucleotide-binding pocket of normal cellular ras proteins. These mutations produce proteins with

reduced intrinsic capacity for hydrolyzing guanosine triphosphate (GTP) and, consequently, markedly diminished sensitivity to a GTP-ase-activating regulatory protein. Expression of these activated ras proteins causes malignant transformation of cells in vitro and contributes to oncogenesis in animals. Bourne also stated that cAMP can stimulate, inhibit, or have no effect on proliferation. It is already known that cAMP stimulates hGH secretion and proliferation of somatotropes. Other tropic hormones that use cAMP as a second messenger include the thyroid, adrenal, and sex glands. It is easy to imagine that tumors of these glands might result from the activation of mutations in  $G_s$  protein or in other elements of the cAMP-signalling pathway.

Further speculation might be in order. Could the McCune-Albright syndrome, characterized by sexual precocity, cafe-au-lait spots, and polyostotic fibrous dysplasia, result from abnormal or mutated  $G_s$ ? We may know the answer in a few years.

Robert M. Blizzard, M.D.

were as low as 1.9 mmol/L 38 hours after GH injections; a simultaneous plasma IGF-I level was 360 U/L, compared with 130 U/L prior to the start of therapy. Fasting plasma glucose levels remained low when the child was given thrice-weekly injections of non-methionyl GH, but he was not hypoglycemic.

The third child, also a male with panhypopituitarism, exhibited hypoglycemia on the first day of life and was treated with thyroxine and hydrocortisone. Thrice-weekly injections of methionyl GH were begun when he was one year old. Like the other two children, he also experienced hypoglycemia, with blood glucose levels as low as 2.3 mmol/L 36 hours after each injection. Treatment with daily in-

jections resulted in complete resolution of hypoglycemic symptoms.

The authors suggest that the high levels of somatomedin-C (IGF-I), which often fail to peak until 19 hours after GH injection, contribute to the total insulin-like activity in the serum since they are not accompanied by GH, which would usually antagonize the glucose-lowering effects of insulin.

Press M, Notarfrancesco A, Genel M. *Lancet* 1987;1:1002-1004.

**Editor's comment**—These interesting case reports suggest that all patients requiring GH therapy, even those who do not initially present with hypoglycemia, should be carefully observed for the presence of low blood glucose

levels when receiving thrice-weekly GH injections.

Haymond et al (JCEM 1976;42:846) previously demonstrated that the hypoglycemia observed in untreated patients with panhypopituitarism is substrate-mediated and characterized by low circulating concentrations of plasma alanine and glutamine. However, these patients, when receiving cortisone and daily GH injections, did not become hypoglycemic after 30 hours of fasting. No subject receiving GH every third day was studied. From the data presented by Press et al, it would seem reasonable to repeat Haymond's fasting study with more traditional GH therapy and measurements of IGF-I.

William L. Clarke, M.D.

## Short-Term Testosterone Treatment at Bone Age 12-13 Years Does Not Reduce Adult Height in Boys with Constitutional Delay of Growth and Adolescence

Zachmann, Studer, and Prader retrospectively compared the adult heights of two groups of males with constitutional delay of growth and adolescence (CDGA). The first group (22 patients) had received no therapy. The second group (19 patients) had been treated with long-acting testosterone, at a dose of 100-250 mg/month for periods of 2-45 months. Target height calculations (mid-parental heights) and predicted heights (calculated by three methods) were used.

The mean adult height was not compromised in the treated group, but was comparable with or exceeded the predicted heights for both groups. The authors conclude that there was no correlation of the total testosterone dose (absolute and corrected for surface area) with adult height and with the differences between the three height predictions and adult height. The authors also state that the fear that testosterone treatment might later impair gonad function and fertility is not warranted.

Zachmann M, Studer S, and Prader A. *Helv Paediatr Acta* 1987;42:21.

**Editor's comment**—These analyses are for groups and not individuals, which limits their value somewhat. One must be cautious in using mean data for groups and applying the interpretation of those data to treatment of individuals. For example, a minority of patients may grow markedly and a majority grow moderately less than the mean for the group. This can be interpreted to mean that treatment may be contraindicated for most

## Does Growth Hormone Cause Relapse of Brain Tumors?

This report compares tumor relapse rates in two groups of patients: 31 growth hormone (GH)-treated patients with brain tumors distant from the hypothalamic-pituitary axis and all patients with similar tumors in the North-West Tumor Registry between 1972 and 1982. Those in the latter group did not receive GH.

Patients treated with GH for growth failure secondary to cranial irradiation included 14 with medulloblastoma, eight with glioma, two with ependymoma, six with leukemia, and one with T-cell lymphoma. Five relapses occurred: one optic nerve glioma, two medulloblastomas, and two ependymomas. Three relapses occurred during GH therapy, and two occurred after GH therapy was completed. The relapse and survival rates, which were presented according to tumor type, indicated that GH therapy did not increase the risk of tumor relapse. Patients treated with GH did not have more relapses, either during or after discontinuation of therapy, than those who did not receive GH. Patients who relapsed tended to be older at

patients with the condition under consideration. Therefore, caution is urged in using mean data of groups to determine therapeutic approaches. I invite the authors to write to Growth, Genetics, and Hormones and supply data on individuals and/or comment more fully on their study findings.

The authors' statement regarding the absence of long-term effects of testosterone therapy is related not to patients in this study but to data published elsewhere by Zachmann et al (J Pediatr 1976;88:116).

The authors' findings may be in accord with those of Martin et al [published in Illig R, ed: *Pediatr Endocrinol*, and Visser HKA, ed: *Acta Endocrinol* (1986;Suppl:279)].

diagnosis and have slightly later onset of puberty.

Clayton PE, Gattamaneni HR, Shalet SM, et al. *Lancet* 1987;1: 711-713.

**Editor's comment**—This paper presents important information for physicians caring for children who have received cranial irradiation and have subsequently developed growth failure. Although a significant number of patients with central nervous system (CNS) tumors will experience relapse, it is reassuring that those treated with GH do not appear to be at increased risk. However, as the prognosis for patients with CNS tumors begins to improve, it is important to identify the long-term sequelae associated with either the tumor or GH treatment of growth failure. For those receiving craniospinal irradiation, hypothalamic pituitary dysfunction is common. There is often a reluctance to begin GH therapy in these patients, since it has been considered by some to contribute to tumor regrowth or relapse. The findings of the present study suggest that GH treatment does not increase this risk.

William L. Clarke, M.D.

Martin et al examined individual data and group data. They concluded that a monthly dose of 50 or 100 mg of testosterone cypionate for approximately 9-12 months did not diminish predicted height, although a dose of 200 mg/month was associated with a trend toward stature that was lower than predicted.

My approach to therapy for patients with CDGA is to use a monthly dose of only 50-100 mg of testosterone enanthate for 6-12 months and only in boys 14 years of age and older. Younger boys are better treated with oxandrolone ( $\leq 0.1$  mg/kg body weight/day).

Robert M. Blizzard, M.D.

## Tubular Bone Alterations in Familial Short Stature: Two Reports

Familial short stature (FSS) accounts for about 50% of the children who are seen by pediatric endocrinologists for assessment of growth. These children usually are in good health, have no obvious dysmorphology, and grow at a consistently normal rate. Growth usually proceeds parallel to the 5th percentile, and the predicted adult height is within range for the child's family. Essentially, these patients are short because their parents and families are short. Since such children are considered "normal," their skeletal anthropometric characteristics are presumed to be similar to those in the rest of the "normal" population.

In these two reports, however, a high prevalence of skeletal alterations in individuals with FSS was noted. The occurrence of these characteristics has not been reported previously in this patient group.

A detailed anthropometric study was performed in 40 white children with FSS. Measurements were compared with those from 40 children of normal stature who were matched for age, race, and sex, and from 958 adolescent boys and girls with normal stature. Anthropometric measurements were also obtained from 30 short parents of FSS children and compared with those from 26 normal-statured parents with FSS children and from 33 unrelated normal-statured adults.

Shortening of the fifth metacarpal bone was more prevalent in the 40 FSS children (78%) than in the children with normal stature (28%) and the healthy adolescents (39%,  $P < 0.001$ ). Rhizomelia was also more prevalent in all FSS children (42%) than in the children with normal stature (15%,  $P < 0.01$ ) and the healthy adolescents (17%,  $P < 0.001$ ). Likewise, shortening of the fifth metacarpal bone was more prevalent in the short parents

of the FSS children (73%) than in the unrelated adults with normal stature (27%,  $P < 0.001$ ). Also, the prevalence of rhizomelia was higher in the short parents of the FSS children (33%) than in the unrelated adults with normal stature (12%,  $P < 0.05$ ).

Disproportionate shortening of the lower limbs was more prevalent in the FSS children (32%) than in the healthy adolescents (11%,  $P < 0.001$ ). Disproportionate shortening of the arms was more prevalent in the FSS children (35%) than in children with normal stature (10%,  $P < 0.01$ ) and healthy adolescents (8%,  $P < 0.001$ ).

The presence of more than one form of tubular bone alteration occurred more frequently in the children and adults with FSS than in the groups with normal height. Most children and adults with FSS had one to four types of tubular bone alteration, while the majority of individuals with normal stature had either no tubular bone defect or only one type of this defect.

In view of the high prevalence of brachymetacarpia V in FSS patients, the authors also performed detailed radiologic anthropometry of the hand in 28 FSS children. Lengths of each of the hand bones were measured and compared with the normal standards developed by Garn and Poznanski. Moreover, the fifth metacarpal was compared with the other metacarpal bones by obtaining ratios and comparing these ratios with the normal standards set by Garn.

The results of this latter study revealed that most patients with clinical brachymetacarpia V had radiologic evidence of fifth metacarpal bone shortening. The metacarpal pattern profiles of the patients with and without brachymetacarpia V differed. The shortest metacarpal bones in children with clinical brachymetacarpia V were the first and fifth, while in the children without clinical brachymetacarpia V, the shortest metacarpal bone was the fourth, followed by the third and fifth. The

phalangeal pattern profiles of these two groups were similar.

The ratios between the fifth metacarpal and the other metacarpal bones in the children with brachymetacarpia V showed that the fifth metacarpal bone was short in relation to the third and fourth metacarpal bones, while the opposite was true in the group without clinical brachymetacarpia V. Moreover, it was also observed that there is a significant positive correlation between height reduction and metacarpal and proximal phalangeal bone shortening in the group with clinical brachymetacarpia V. There was no correlation between height reduction and the length of the distal and middle phalanges.

Cervantes C, Lifshitz F. *Human Biology* 1988;60:151-165. Cervantes C, Lifshitz F, Levenbrown J. *Pediatr Radiol* 1988;18:248-253.

**Editor's comment**—The results of these two studies indicate a very high prevalence of tubular bone alterations, mainly disproportionate shortening of the limbs, rhizomelia, brachymetacarpia V, and possible brachymetacarpia I, in children and adults with FSS. Since these characteristics are frequently seen in various syndromes characterized by skeletal dysplasia, it seems reasonable to speculate that children who fall in the lower end of the normal growth standards are short statured because of an inherited abnormality in endochondral growth, the major process responsible for increase in stature. The possibility of mild hypochondroplasia in FSS patients cannot be entirely ruled out, since this condition can present with no stigmata other than short limbed FSS and brachydactyly. There are isolated reports of families with dominantly inherited brachymetacarpia and short stature but no other associated abnormalities. The presence of brachymetacarpia V in the parents of

*continued on page 14*

**continued from page 13**

affected FSS children suggests an autosomal dominant mode of inheritance of this characteristic. This trait is also fairly common even in the normal population. Therefore its association with FSS may be coincidental. However, since these tubular bone alterations were significantly more prevalent in the FSS children and their parents and siblings than in the normal population, an inherited trait is most likely responsible for these pleiomorphic manifestations. Segregation analysis may help determine the mode of inheritance of these skeletal alterations.

The findings in these two studies illustrate the major role that endochondral ossification plays in de-

termining stature by expressing itself not only in overall height but also in disproportionate shortening of tubular bones in those with FSS.

The presence of tubular bone alterations in an otherwise healthy patient with FSS should be carefully evaluated before instituting therapy with growth hormone (GH). This is especially important since GH is now available in unlimited supply and pressure to treat the short child with the drug is again high. It may be reasonable to expect that children with FSS who also have skeletal abnormalities would respond less favorably to GH or require a higher dose of GH than would those with FSS and no bone abnormalities.

Fima Lifshitz, M.D.

### Parental Health Beliefs as a Cause of Nonorganic Failure to Thrive

Parental health beliefs and misconceptions about the constituents of a normal diet for infants are reported as a cause for failure to thrive in seven children (four male, three female), aged 7 to 22 months, who were evaluated for poor weight gain and deteriorating linear growth.

After a medical and nutritional evaluation, it was found that the caloric intake for these children had been restricted by their parents to such a degree that they were receiving much less than the recommended caloric allowance for their age and sex.

The parents instituted diets that were consistent with health beliefs that are currently in vogue and recommended by the medical community for adults who are obese or at risk for cardiovascular disease or both. These parents were concerned that their children would become obese, develop atherosclerosis, become dependent on junk food, or develop eating habits that the parents felt were unhealthy. However, these diets resulted in inadequate

weight gain and a decreased linear growth rate in the infants.

Nutritional counseling was provided, all unnecessary food restrictions were lifted, and the caloric intake was increased to the recommended allowance for age. The weight gain rate increased soon thereafter, and the linear growth rate increased within three months of improved nutritional therapy.

Exaggerated parental concerns over excessive food intake in childhood have resulted in additional cases of failure to thrive during infancy.

Pugliese M, Wyman-Daum M, Moses N, Lifshitz F. *Pediatrics* 1987;80:179.

**Editor's comment**—In the past few years, we have heard from many self-appointed experts in child care and nutrition who advocate numerous and often unsubstantiated "health beliefs." This report demonstrates what can happen if this "advice" is followed without appropriate medical supervision. Fear of obesity is quite prevalent in our population, and parents are well aware of the commonly held belief that if obe-

### Recovery From Post-Traumatic Anterior Pituitary Insufficiency

Usually, it is assumed that traumatic damage to the hypophysis persists and is barely reversible, except when the damage is due to an acute condition, such as diabetes insipidus. Eiholzer et al describe a patient in whom the sequelae of a severe trauma disappeared after many years.

At 7 years of age, the patient was in a car accident and was comatose for four months. His condition improved after insertion of a ventriculo-atrial shunt. A discrete spastic tetraparesis persisted, as did insufficiency of the anterior hypophysis, which led to

sity occurs in infancy it may persist throughout life. This may not be true, but it can certainly lead to unnecessary dietary restrictions in infancy nonetheless. Similarly, following a "healthy diet" to prevent atherosclerosis and eliminating so-called "junk food" from the diet are also very prevalent and are endorsed by the medical community. Even though the American Academy of Pediatrics and the American Medical Association have never endorsed low-fat, low-calorie diets for infants younger than 2 years of age, parents with misguided health beliefs have enforced these dietary recommendations for their infants, who then fail to thrive.

Junk food is an abused term. Indeed, there is no junk food, but there may be junk diets. High-calorie snacks are necessary for children, since they contribute up to one third of a child's usual dietary intake. A cookie or a chocolate sundae may be necessary and appropriate if the remainder of a child's diet is well-balanced. Eliminating these high-calorie snacks could result in an inability to ingest the calories that are necessary for growth in childhood.

Fima Lifshitz, M.D.

progressive growth retardation. The provocative tests showed an unsatisfactory response to growth hormone (GH). Plasma testosterone was low, and a secondary hypothesis was established. The child received replacement therapy for his endocrine deficiencies, and his growth rate was promptly normalized. A spontaneous increase in testicular volume was observed when the patient was 17 years old, and treatment with testosterone and human growth hormone (hGH) was discontinued. Two years later, treatment with thyroxine was stopped.

Eholzer U, Zachmann M, Gnehm HE, Prader A. *Eur J Pediatr* 1986; 145:128-130.

**Editor's comment**—Post-traumatic deficiencies of the adeno-hypophysis arise in the following different ways: through hypothalamic lesions, following denervation due to damage of the stalk, by interruption of the long portal vessels, and by lesions directly affecting the anterior lobe. In the present case, the hypothalamic origin of the hormone deficiency could be excluded since the administration of thyrotropin-releasing hormone (TRH) did not produce an increase of thyroid-stimulating hormone (TSH). Apparently the pituitary was touched directly. The presupposition for the gradual recovery that was observed is the re-innervation of the stalk, the recanalization of the portal vessels, the regeneration of the necrotized pituitary tissue, or a combination of these (as shown in animal experiments conducted by Daniel and Prichard in 1975). The observation is especially important to the clinician, since it demonstrates that the pituitary may not be permanently damaged after a severe acquired lesion and that the function of the gland should be checked repeatedly after such a trauma.

Jürgen R. Bierich, M.D.

## Gross and Fine Motor Development in 47,XXY and 47,XYY Males

Males with sex-chromosome anomalies come to the clinician's attention because of their tall stature, as seen in those with Klinefelter syndrome, gynecomastia, and hypogonadism. In an ongoing study to define the natural history of children with sex-chromosome abnormalities, 14 boys with XXY and four with XYY were compared with matched controls.

Neuromuscular deficits, such as motor awkwardness and slow movement, were described in early childhood and continue to be present in the school-age boys. XXY boys have significantly lower mean scores for limb coordination, speed, dexterity, and gross motor activity than the matched controls. School intervention for reading deficiency had occurred in 15 of the 18 boys with aneuploidy in contrast with none of the 14 controls. In addition, auditory processing deficits and dyslexia were believed to play a greater role in decreased school performance than would have been expected. Hypermobility of the finger joints

and poor grasp seemed to hinder writing skills.

Findings from this study suggest that mild to moderate dysfunction in sensory motor integration occurs frequently in boys with sex-chromosome aneuploidy and is likely to be an additional factor that influences classroom performance.

Salbenblatt JA, Meyers DC, Bender BG, et al. *Pediatrics* 1987; 80:240.

**Editor's comment**—As the authors point out, these mild changes found in males with sex-chromosome aneuploidy can have a significant influence on both classroom performance and social integration of self-concept and adequate peer interaction. Clinicians must be aware of these problems and institute early intervention when they are recognized. Perhaps males with neuromuscular deficits such as those described should be screened by buccal smear determinations for the presence of Barr bodies and double quinacrine bodies. This could make an appropriate study.

Judith G. Hall, M.D.

## Life Expectancy in Down Syndrome

Life expectancy among patients with Down syndrome may be much higher than suspected, based on data from 1,341 Down syndrome patients in the British Columbia Health Surveillance Registry from 1952 to 1981. The important factor seems to be the presence or absence of congenital heart disease.

Among Down syndrome patients with congenital heart disease, 23% died during the first year of life and only 53% survived to age 20. In contrast, 90% of Down syndrome patients without congenital heart disease survived

to age 1 year and almost 80% survived to age 30. Clearly, patients with Down syndrome and congenital heart disease have a disproportionately higher mortality than those without congenital heart disease, particularly during the first year of life.

Baird PA, Sadovnick AD. *J Pediatr* 1988;110:849.

**Editor's comment**—These data are very important for pediatricians caring for children with Down syndrome, since families need assistance in planning appropriately for the child's lifetime and life expectancy.

Judith G. Hall, M.D.

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## MEETING CALENDAR

**July 8-10** International Symposium on the Marfan Syndrome. Baltimore, Maryland. Contact: Diane Heydinger, Johns Hopkins University School of Medicine, 720 Rutland Road, Baltimore, MD 21205 (301-955-2959)

**July 10-13** 20th Anniversary of the Clinical Genetics Conference. Baltimore, Maryland. Contact: Carita Kearney, Johns Hopkins University School of Medicine, 720 Rutland Road, Baltimore, MD 21205 (301-955-2959)

**July 17-23** 8th International Congress of Endocrinology. Kyoto, Japan. Contact: Travel Planners—Kyoto Congress, Suite 150, GPM Building, San Antonio, TX 78216-5674 (512-341-8131)

**July 20-23** 15th International Auxology Congress. Exeter University, Exeter, England. Contact: Prof. J.M. Tanner, Room 115, Institute of Child Health, 30 Guilford Street, London, England WC1N 1EH

**October 15-20** 57th Annual Meeting of the American Academy of Pediatrics. San Francisco, California. Contact: American Academy of Pediatrics, 141 Northwest Point Boulevard, PO Box 927, Elk Grove Village, IL 60009 (800-433-9016 outside Illinois, 800-421-0589 in Illinois)

**October 27-31** 40th Postgraduate Assembly of The Endocrine Society. Franklin Plaza Hotel, Philadelphia, Pennsylvania. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

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# GROWTH

## Genetics & Hormones

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## Renal Disease and Growth Retardation

David R. Powell, M.D.  
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Baylor University School of  
Medicine  
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Many individuals who develop chronic renal failure (CRF) as children fail to achieve an adult height consistent with their genetic potential.<sup>1</sup> Moreover, they often do not achieve a final height that is within the normal range despite delays in bone age and in the onset of pubertal development, events that should allow a prolonged period of growth to occur.<sup>1,2</sup>

While there is wide variability in the level of residual renal function capable of maintaining normal growth, the risk for growth failure probably increases when residual function is less than 30% of normal for age.<sup>3</sup> The lowest growth rates and the greatest losses of growth potential occur in infants with CRF.<sup>2,3</sup> Growth rates are also subnormal for older children with end-stage renal disease who are treated with hemodialysis<sup>4</sup> and probably for those treated with peritoneal dialysis as well.<sup>4,5</sup> In contrast, older children with milder degrees of CRF who do not require dialysis grow at rates that are closer to normal.<sup>2</sup> Interestingly, growth rates of children who have received renal transplants are usually not above the norm for age. However, the mean rate has steadily improved in recent years, especially with the advent of cyclospor-

ine therapy.<sup>5,6</sup> Of perhaps the greatest significance, catch-up growth is rarely observed either in children with CRF or in those with a renal transplant.<sup>2</sup>

Many factors contribute to growth failure in children with CRF. These factors are listed in the Table on page 2 and discussed in some detail below.

### Hormonal Imbalance

The hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axes are two major endocrine systems that interact with growth-plate cartilage to regulate growth. Each axis is perturbed in individuals with CRF, and the uremic milieu may also directly impair the function of growth-plate cartilage itself. While mild hypothyroidism in adults with CRF results from abnormalities at multiple levels of the hypothalamic-pituitary-thyroid axis,<sup>7</sup> children with CRF nevertheless appear to be clinically euthyroid.<sup>8</sup> In contrast, the hypothalamic - pituitary - gonadal axis does appear to be compromised in children with CRF. At first, hypogonadotropic hypogonadism persists and puberty is delayed; later, hypergonadotropism is found.<sup>7</sup> These abnormalities do not necessarily lead to a significant shortfall in final height, however, since children with CRF often exhibit normal pubertal growth spurts.<sup>2</sup>

The growth hormone (GH)-insulin-like growth factor (IGF) axis is probably the major hormonal sys-

tem regulating bone growth. Apparently, these two hormones act in concert to produce growth: GH stimulates both differentiation of chondrocyte precursors in growth-plate cartilage and IGF-I production by many tissues including cartilage; IGF-I then stimulates clonal expansion of these differentiating chondrocytes.<sup>9</sup> GH levels are elevated in adults and children with CRF, probably because of GH overproduction.<sup>7,10</sup> Although past data suggested that IGF levels were low in CRF patients, recent work indicates that these earlier IGF measurements were in error,<sup>11</sup> and concludes that IGF-I and IGF-II levels are normal or increased in adults and growth-retarded children with CRF.<sup>11-14</sup> These data suggest that children with CRF may be resistant to the growth-promoting action of these two hormones. Alternatively, GH or IGF may be carbamylated or otherwise modified by the uremic milieu so that their biologic potency is decreased.

### Energy Malnutrition

Inadequate energy intake clearly contributes to growth failure in

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## Renal Disease and Growth Retardation

*continued from page 1*

children with CRF, especially during infancy, when higher energy requirements for each kilogram of body weight are frequently not met.<sup>2,3,15,16</sup> Children and infants with CRF and severe associated malnutrition often respond to dietary supplements with improved growth, although gastrostomy or nasogastric feedings are often required in infants to ensure adequate energy intake.<sup>16</sup>

**Table.** Factors contributing to growth failure in children with chronic renal failure

Hormonal Imbalance
GH-IGF axis
Hypothalamic-pituitary-thyroid axis
Hypothalamic-pituitary-gonadal axis
Energy Malnutrition
Uremic Toxins and Inhibitors of Hormone Action
Renal Osteodystrophy
Sodium Bicarbonate Wasting
Sodium Chloride Wasting
Hyposthenuria
Prednisone Therapy
Psychosocial Dysfunction
Hypertension
Anemia

Rat models of CRF also demonstrate the association of malnutrition and growth failure: CRF rats eat much less food and gain much less weight and length than sham rats fed ad lib. However, malnutrition is not the sole cause of growth failure, since CRF rats gain significantly less weight and length than their pair-fed counterparts despite comparable energy intake.<sup>17,18</sup>

Indeed, malnutrition does not seem to be the major cause of growth delay in many children with CRF, since they often fail to grow better even when given dietary supplements.<sup>16</sup> In one study, only those children who initially ingested less than 75% of the recommended calories for age responded to caloric supplements

with improved growth, and growth velocities above the mean for age were rare.<sup>15</sup>

The way low energy intake causes growth failure is not understood, although a direct inhibitory effect on growth-plate chondrocyte metabolism seems likely. Energy malnutrition is also associated with high serum GH and low serum IGF-I levels; since growth improves and these levels return to normal with nutritional rehabilitation, it is possible that the effects of malnutrition on growth are modulated by IGF-I. However, energy-deficient and growth-retarded individuals with CRF have normal IGF-I levels, suggesting that malnutrition does not cause growth failure in CRF by affecting the GH-IGF axis.<sup>12,17,18</sup>

### Uremic Toxins and Hormone Inhibitors

CRF is associated with the accumulation or increased production of many molecules, some of which may directly impair growth. Phillips et al<sup>14</sup> found increased levels of a 1 kiloDalton (kD) molecule in uremic adult serum. This poorly characterized substance is a generalized inhibitor of cartilage metabolism that blocks the growth stimulating effects of IGFs and other growth factors.

Also, IGF-binding protein activity and radioimmunoassay (RIA) levels of IGF-binding proteins are increased in the serum of CRF patients.<sup>12,19</sup> Recent evidence suggests that a purified 25 kD IGF-binding protein<sup>20</sup> markedly inhibits the growth of fetal cartilage in organ culture (Powell et al, unpublished observations). Further work will establish whether these uremic toxins and inhibitors contribute to growth failure in vivo and whether inhibitor levels are affected by malnutrition or by high protein intake.

### Renal Osteodystrophy

The inability of damaged kidneys to excrete excess phosphate and to synthesize 1,25 dihydroxyvitamin D leads to renal osteodystrophy (ROD) and associated secondary hyperparathyroidism.

Poor growth may be the result of disturbed cartilage metabolism and/or frank bony deformities. Radiologic and biochemical evidence of ROD is seen more often in short children and in those with renal function that is less than 20% of normal. However, evidence of ROD is often found in children with CRF who have normal height, while short children with CRF frequently have no signs of ROD.<sup>21</sup>

Treating older CRF children with phosphate restriction and vitamin D derivatives can result in accelerated growth, often by healing frank skeletal deformities, but true catch-up growth is rare.<sup>16,22</sup> However, preliminary studies suggest that children under 2 years of age who are treated with calcitriol grow at more normal rates. This therapy, then, may prevent some of the lost growth potential that usually occurs in infants with CRF.<sup>22</sup>

### Bicarbonate, Salt, and Water Losses

Children with obstructive or dysplastic renal disease and CRF often have renal tubular dysfunction and excessive urinary loss of sodium bicarbonate, sodium chlo-

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ride, and water. Children who are otherwise normal but have renal wasting of bicarbonate and chronic hyperchloremic metabolic acidosis grow poorly. The physiology responsible for this poor growth is unknown, but complete catch-up growth often occurs with oral bicarbonate therapy.

Growth failure can also occur when salt wasting leads to dehydration or when hyposthenuria leads to hypertonicity. In these cases, replacement therapy with salt or water should improve growth. Although these fluid and electrolyte disturbances can be effectively treated, salt and water wasting are sometimes difficult to diagnose, and all of these disorders can be difficult to manage in infants with CRF.<sup>2,16,23</sup> Undoubtedly, poor management of these disorders during infancy can lead to permanent loss of growth potential.

### Prednisone and Other Factors

Prednisone therapy, which is most often used in children with kidney disease for post-transplant immunosuppression, causes growth failure in a dose-dependent fashion. The mechanism for this growth failure is not clear, but it is thought that prednisone may directly damage chondrocytes or stimulate production of generalized inhibitors of cartilage metabolism.<sup>24</sup> Unfortunately, higher doses are used in those patients who have lost some degree of renal function due to episodes of graft rejection, and persistent growth failure is common in these individuals. Recently, it has been recognized that immunosuppression with cyclosporine permits the prednisone dosage to be lowered or discontinued, resulting in improved or catch-up growth in some transplanted children.<sup>6</sup>

Psychosocial problems may contribute to poor growth in some children with CRF.<sup>2</sup> Severe hypertension and anemia have been implicated as well. Further study is needed to evaluate the extent of the contributory roles of these factors in growth delay in these children.

### Treatment and Catch-Up Growth

In the past few years, pediatric nephrologists have aggressively attempted to maximize growth in infants with CRF. Most nephrologists now feel that infants and even older children with reduced renal function will remain short for chronologic age despite aggressive therapy to correct energy malnutrition, renal osteodystrophy, acidosis, salt wasting, and hyposthenuria.

Research continues into the factors responsible for this persistent growth failure. However, the almost uniform lack of catch-up growth in children with CRF is striking, suggesting that the mechanism for catch-up growth may be directly affected in these children. Unfortunately, the physiologic basis for catch-up growth is poorly understood.<sup>25</sup> Although the GH-IGF axis does not appear to play a major role in catch-up growth, and despite the fact that GH levels are already elevated in individuals with CRF, preliminary studies in children with CRF<sup>26</sup> and rats<sup>18,27</sup> show a short-term improvement in growth for those individuals receiving GH therapy.

These data suggest the need for long-term studies to examine whether GH therapy produces sustained catch-up growth in CRF children, and whether this treatment is associated with complications such as insulin resistance, worsening ROD, or accelerated decline in residual renal function. Growth data from these and other studies must be collected at optimal times and are best presented as growth velocity standard deviation scores (GVSDS). As Barrett et al<sup>1</sup> clearly demonstrate, GVSDS are most likely to demonstrate whether GH or any other therapy is associated with normal or catch-up growth in children with CRF.

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### In Future Issues

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Anabolic Steroids in Athletes:  
Efficacy or Fantasy?  
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The Role of Mosaicism and  
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and Human Disease  
by Dagmar Kalousek, M.D.

# Lipodystrophy

William L. Clarke, M.D.  
*Associate Editor*  
*Growth, Genetics, and Hormones*

Lipodystrophy is a term used interchangeably with lipoatrophy to describe a group of rare disorders characterized by hyperlipidemia, marked insulin resistance, and the absence of subcutaneous fat. Three lipodystrophic syndromes have been described: congenital or total lipodystrophy, total acquired lipodystrophy, and partial acquired lipodystrophy (Table). These are categorized on the bases of genetic inheritance, distribution of fat loss, and the age of onset.

*Congenital or total lipodystrophy* is an autosomal recessive disorder characterized by a generalized lipodystrophy that is present from birth. *Total acquired lipodystrophy* occurs sporadically and is not present at birth. *Partial acquired lipodystrophy* also occurs sporadically, but fat loss is confined to a single area of the body. Associated findings in all of these disorders include advanced height and bone age in childhood, hepatomegaly, and acanthosis nigricans. In addition, some individuals exhibit enlarged genitalia, and females may have polycystic ovarian disease. Systemic cystic angiomyomatosis, idiopathic hypertrophic subaortic stenosis, glomerulosclerosis or glomerulonephritis, pancreatitis, and thyroiditis also have been reported. Although statistical analyses are lacking, the prognosis for persons with these disorders is poor, with most affected individuals dying of the complications of liver disease in early adulthood.

Exemplary of congenital total lipodystrophy are three siblings whom we have had the opportunity to study over a period of 12 years at the University of Virginia Children's Medical Center. The oldest sibling, a female, presented at 3 years of age with hepatomegaly, total absence of subcutaneous fat, acanthosis, hyperlipidemia, and an

advanced bone age. Absence of fat and a protuberant abdomen had been noted by the mother when the child was 3 months old. By 13 years of age, she had developed insulin-resistant diabetes mellitus, virilization with clitoromegaly, polycystic ovarian disease, thyroiditis, proteinuria, and cystic angiomyomatosis. By age 20 she had also developed idiopathic hypertrophic subaortic stenosis.

The next-born sibling, also female, presented at 9 months of age with fat wasting, hepatome-

extreme heterogeneity of the disorders make it difficult to characterize or rigorously evaluate the etiology or pathogenesis of these syndromes.

If a primary absence of fat cells were etiologic, then excess carbohydrate would be stored as glycogen, metabolized to lactate or triglycerides, or circulated in the bloodstream as glucose.<sup>1</sup> This, however, does not explain the presence of insulin resistance, virilization, or other associated findings.

**Table.** Lipodystrophic syndromes

Type	Inheritance	Distribution of fat loss
Congenital	Autosomal recessive	Total
Total acquired	Sporadic	Total
Partial acquired	Sporadic	Confined to single area

megaly, acanthosis, and hyperlipidemia. During her teenage years, she also developed virilization, polycystic ovarian disease, insulin-resistant diabetes, thyroiditis, cystic angiomyomatosis, and idiopathic hypertrophic subaortic stenosis. The third affected sibling, a male, presented at 6 years of age with subcutaneous fat wasting, acanthosis, and advanced height and bone age. Currently 18 years of age, he has yet to develop diabetes or hyperlipidemia.

## Pathogenesis and Etiology

The pathogenesis of the lipodystrophic disorders remains unclear. Various studies have suggested a variety of possible etiologies including a primary absence of fat cells, the presence of a lipolytic or insulin-antagonizing factor, hypothalamic/pituitary disease, and insulin-binding abnormalities. However, none of these can explain all of the abnormalities seen in these disorders. In addition, the limited numbers of patients available for study and the

Taton et al<sup>2</sup> extracted both a lipid-mobilizing factor (Chalmers factor) and an insulin-antagonizing factor (Louis factor) from the urine of a patient with total acquired lipodystrophy. When injected into normal mice, these factors produced hyperlipidemia and fatty infiltration of the liver as well as insulin resistance. In addition, injection of Chalmers factor produced hyperglucagonemia, which is known to be lipolytic and associated with carbohydrate intolerance. In contrast, Louis factor prevented the storage of triglycerides in adipocytes. Studies by other investigators, however, have not confirmed the existence of these factors in all patients.

Data from several studies led to the suggestion that lipodystrophy might be caused by a disturbance of the hypothalamic/pituitary axis.<sup>3</sup> Lack of growth hormone (GH) release following pharmacologic stimuli or during sleep, an acromegalic appearance, detectable levels of hypothalamic-releasing factors in the peripheral plasma, hyperprolactinemia, pres-

ence of both elevated basal and nonsuppressible adrenocorticotrophic hormone, and hyperresponsiveness of thyroid-stimulating hormone to thyrotropin-releasing hormone have been reported. In addition, Louis factor has been thought to be of pituitary origin. However, hypophysectomy has not reversed the metabolic or physical abnormalities associated with lipodystrophy.<sup>4</sup>

The lipodystrophic disorders share common features of extreme insulin resistance, virilization, and acanthosis in both obese and nonobese women with polycystic ovarian disease. In these syndromes, androgen levels correlate directly with the degree of insulin resistance. However, the etiologic relationship between the two findings remains unclear.

Kahn et al<sup>5</sup> studying insulin binding in patients with extreme insulin resistance and acanthosis nigricans, have described two types of binding abnormalities and used them to classify patients with insulin resistance and acanthosis. Type A patients demonstrate a decrease in number of receptors or possibly a post-receptor defect and are characterized by onset of symptoms in childhood, with virilization and polycystic ovarian disease occurring typically. Type B patients display antibodies against the insulin receptor. These patients acquire their disorder later in life than do those with type A insulin resistance. Androgen excess in type B patients is unusual. Harrison et al<sup>6</sup> have recently reported the presence of a circulating inhibitor of insulin's action after it has been bound to its receptor in a patient with insulin resistance, acanthosis, and polycystic ovaries without lipodystrophy. How these studies in patients without lipodystrophy, but with many of the same clinical findings of the three lipodystrophic syndromes described above, are related to the lipodystrophies remains to be determined.

Oseid et al<sup>7</sup> however, have demonstrated a decrease in binding affinity of insulin to the receptors on monocytes in congenital

lipodystrophy, and Kriauciunas et al<sup>8</sup> recently demonstrated a 50% decrease in insulin binding in the three patients with congenital lipodystrophy who were presented above. Using restriction fragment endonucleases, Kriauciunas et al have also demonstrated a unique defect in the portion of the insulin receptor gene that codes for the receptor's alpha subunit in these three siblings, but not in one of their nonaffected siblings nor in more than 100 normal controls or patients with diabetes. How this finding relates to lipodystrophy, acanthosis, virilization, polycystic ovaries, and the myriad of other abnormalities associated with lipodystrophy is not known, but the discovery of a unique genetic defect in this family raises the prospect of being better able to understand the etiology of the lipodystrophic syndromes.

### **Skeletal Maturation and Growth Velocity**

The etiology of advanced skeletal maturation and accelerated growth velocities in children with lipodystrophy has not been clarified. Undoubtedly, the elevated prepubertal androgen levels described in some individuals with lipodystrophy contribute to the advanced skeletal maturation and accelerated growth. However, the acromegaloid appearance of some of these individuals has led to investigations of GH secretion in lipodystrophy. In our patients, the mean 24-hour integrated GH levels were within the normal range for our laboratory (1.7 to 3.9 ng/mL).<sup>9</sup> Since these studies were performed prior to the advent of GH pulse amplitude analyses, and since somatomedin-C/insulin-like growth factor I concentrations have not been reported in these disorders, it is obvious that further studies are needed.

### **Treatment**

Treatment of patients with lipodystrophy remains difficult and inadequate. Insulin requirements rise to 9,000 U/day and even this dose may fail to normalize blood glucose levels.<sup>10</sup> Caloric restric-

tion to 1,200 or fewer calories/day has been shown to increase insulin sensitivity, improve carbohydrate tolerance, and reduce lipid levels in patients with congenital and acquired lipodystrophy.<sup>11</sup> However, it is rarely possible to achieve the prolonged compliance with dietary therapy that is necessary to evaluate the long-term effects of such therapy on either carbohydrate tolerance or hyperlipidemia.

As stated previously, hypophysectomy fails to restore metabolic or physical abnormalities. Pimozide, an inhibitor of hypothalamic-releasing factors, has been used with limited success.<sup>4,12</sup> Plasmapheresis also has been used to reduce hypertriglyceridemia, but rebound hypertriglyceridemia has been found to occur within seven days.<sup>3</sup>

Fenfluramine, a serotonin inhibitor that was originally marketed to control weight, has some insulin-like activity, which includes reduction of blood glucose concentrations in type II diabetes and elevation of glucose uptake both in the forearm *in vivo* and in adipocytes *in vitro*.<sup>11</sup> In addition, fenfluramine lowers serum triglycerides by inhibiting their absorption and synthesis. Trygstad<sup>13</sup> stated that fenfluramine improved carbohydrate tolerance in patients with congenital lipodystrophy but noted that its use was accompanied by a decrease in caloric intake. In our laboratory, Wilson et al<sup>11</sup> compared the separate effects of fenfluramine and caloric restriction in congenital lipodystrophy. Carbohydrate tolerance improved initially in one of three patients, but the effect was sustained for only four to six weeks. Caloric restriction to 1,200 calories/day produced a much greater improvement in carbohydrate tolerance, but patients did not adhere to the regimen well.

In a recent trial, a dietary medium-chain triglyceride substitution for long-chain fatty acids successfully reduced serum lipid levels, hepatomegaly, and carbohydrate intolerance in a patient

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## Lipodystrophy

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with acquired total lipodystrophy.<sup>14</sup> Medium-chain triglycerides reportedly decrease hepatic glucose production and may directly stimulate insulin secretion. The patient reported in this trial experienced improved carbohydrate tolerance, an 83% decrease in insulin concentrations, a 37% decrease in plasma glucagon levels, and decreases in chylomicron and triglyceride levels, xanthomata, and liver size. This therapy may prove to be effective in others with lipodystrophy, but the long-term effects of a diet that fails to provide essential fatty acids and possibly accelerates premature atherosclerosis remain to be evaluated.

Typically, patients with lipodystrophy present early in childhood with few of the manifestations of the disorder and gradually develop the full constellation of abnormalities by adulthood. Frequently, the loss of subcutaneous fat is the only obvious initial physical finding. Pediatricians are encouraged to examine patients with subcutaneous fat loss carefully and to be aware of the many manifestations of the complicated multisystem lipodystrophic disorders. Until a registry of such patients is initiated and a protocol designed for the systematic evaluation of their physical and biochemical abnormalities, it may not be possible to understand the complex nature of these disorders or to design rational treatment strategies for affected individuals.

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## Letter From the Editor

Dear Colleagues:

Recently, several cases of leukemia in hypopituitary children receiving growth hormone (GH) were reported in *The Lancet* (1988;i:1159). The pediatric endocrinologists of the world and the parents of children receiving GH were most fortunate to have strong leadership from the Lawson Wilkins Pediatric Endocrine Society. The officers appointed a senior committee of pediatric endocrinologists to serve on an ad hoc committee that would speedily accumulate and evaluate worldwide data in this regard and present recommendations to the scientific community.

Drs. Delbert Fisher and Louis Underwood convened a meeting of the committee members. Joining them were Drs. J.C. Job of Paris, who represented the European Society for Pediatric Endocrinology; S. Watanabe of the Cancer Institute in Japan; G. Antony of Australia; H. Dean of Canada; J. Fradkin, R. Miller, and J. Mills of the National Institutes of Health; L. Robison of the Pediatric Oncology Study Group in Minneapolis; and representatives from Eli Lilly, Genentech, Kabi Vitrum, and Serono Corporations. The meeting was cosponsored by the Human Growth Foundation.

After two days of intensive study and consideration, the ad hoc committee concluded that there possibly is a very small increase in the incidence of leukemia in GH-deficient patients treated with GH. On the basis of current evidence, however, the committee could not conclude that GH therapy was responsible for this possible increase. Current estimates indicate that if there is any risk to an individual patient, it is small; patients can be told this. Nevertheless, all patients receiving GH should be followed closely during and after therapy.

It is not my purpose to discuss the data that prompted these conclusions. Readers are encouraged to read the articles and discussions in *The Lancet*. It is my purpose (1) to reassure readers that, with the possible exception of patients in Japan, the increased incidence of leukemia in patients receiving GH is very small, and (2) to publicly express the gratitude of many endocrinologists, parents, and patients to the ad hoc committee members for their tremendous concern, logic, and efficiency.

Obviously, continued observations and collection and reporting of data are essential. However, we have reason to be optimistic in predicting that no significant increase in the incidence of leukemia will be found in association with GH therapy in the future.

For the Editorial Board,  
Robert M. Blizzard, M.D.  
Chairman

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## Growth Without GH: The "Invisible" GH Syndrome

Four children with normal growth velocity, relatively low growth hormone (GH) concentrations as measured by radioimmunoassay (RIA), increased GH concentrations by radioreceptor assay (RRA), markedly increased RRA:RIA ratios, and normal somatomedin C assays were described. These unusual findings suggest the presence of a biologically active GH that is not detected by the usual RIA for GH. Therefore, the structure of the GH molecule in these children is believed to be unusual.

The authors postulate that the

GH molecule(s) secreted by these patients may be a product of the human growth hormone (hGH)-V gene rather than a product of the hGH-N gene, which is normally responsible for GH production. This gene was previously reported by other authors to be unexpressed, since no messenger RNA (m-RNA) derived from it could be detected in human cells.

Bistritzer T, Lovchik JC, Chalew SA, et al. *Lancet* 1988;ii:321.

**Editor's comment**—The hypothesis expressed by the authors is tenable on the basis of the data presented, although not proven. To prove the hypothesis, m-RNA

for the hGH-V gene would have to be demonstrated in the patient(s). The findings are intriguing regardless. Assay measurements in these patients are the opposite of patients previously described by Kowarsky et al (J Clin Endocrinol Metab 1978;47:401); those patients had very low RRA:RIA ratios and slow growth, and were believed to secrete biologically inactive but immunoreactive GH. The four patients reported in the current article resemble some acromegalic patients (reported by Hizuka et al in J Clin Endocrinol Metab 1982;55: 545) who also had significantly higher GH concentrations on RRA than on RIA.

Robert M. Blizzard, M.D.

## Placental Chromosomal Mosaicism Is Responsible for Variations in Growth Rates: Three Reports

If the placentas of children with unexplained intrauterine growth retardation (IUGR) are examined for a chromosomal aneuploidy, a surprisingly large number (perhaps as many as one third of cases of IUGR) will have chromosomal mosaicism confined to the placenta, with a normal cell line and an abnormal cell line. Now that chorionic villus sampling is being done on a regular basis for prenatal diagnosis, it has been found that about 5% of placentas have placental mosaicism with one normal cell line and another with a variety of different chromosomal aneuploidies. These findings suggest that there is a common explanation for IUGR that cannot be attributed to other causes such as maternal smoking or a syndrome: namely, the presence of cytogenetic abnormalities confined to the placenta. Most interesting are the new reports that mosaicism confined to the placenta may also be responsible for allowing fetuses with certain types of chromosomal problems to be carried to term.

Kalousek and McGillivray have recently reported the presence of

a normal cell line in all of the placentas recovered from fetuses with trisomy 18 and trisomy 13 that were born alive. By contrast, trisomic fetuses that are miscarried spontaneously as abortuses or stillbirths do not have mosaicism or cytogenetically normal cells in their placentas. It appears that the normal cell line allows such fetuses to survive long enough to be born alive at term.

Kalousek DK, Dill FJ. *Science* 1983;221:665-667.

Kalousek DK, Dill FJ, Pantzar T, et al. *Hum Genet* 1987;77:163-176.

Kalousek DK, McGillivray BG. *Am J Hum Genet* 1987;41:A278.

**Editor's comment**—Since the placenta is fetal in origin, we have assumed that it has the same chromosomes as the baby. The work described in these reports suggests that 5% of placentas have some cells that are cytogenetically different from those of the baby. When the placenta has abnormal cells but the baby has only normal cells, the baby may have IUGR. When the baby has abnormal cells but the placenta has some normal cells, the abnormal fetus may survive to term.

Judith G. Hall, M.D.

## Mapping and Screening in Families With Multiple Endocrine Neoplasia Type 2A: Four Reports

Recently, multiple endocrine neoplasias type 2A have been mapped to chromosome 10. A number of polymorphic DNA markers around the gene allow prediction in most families of those individuals who are carriers of the gene. In addition, prospective screening annually for manifestations of the disease appears to be effective in prevention of morbidity and mortality. For example, provocative tests to guarantee the release of calcitonin can be used to monitor whether or not "medullary" thyroid carcinoma is present, and 24-hour urine screening for both epinephrine excretion and the ratio of urinary epinephrine to norepinephrine allows detection of proliferation of the adrenal medulla before life-threatening manifestations occur.

An 18-year follow-up study of a large family by Gagel et al suggests that total thyroidectomy, when done at the first appearance of increased calcitonin secretion, is curative since there were no recurrences or metastatic diseases in their patients. Parathyroid dis-

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## Multiple Endocrine Neoplasia Type 2A

### *continued from page 7*

ease seemed to occur only in those patients with well-established medullary thyroid carcinoma or pheochromocytoma. Because more than 50% of affected individuals within the family eventually developed adrenal medullary abnormalities, screening in such families is mandatory.

Sobol H, Saivetti A, Bonnardel C, et al. *Lancet* 1988;i:62.  
Gagel RF, Tashjian AH, Cummings T, et al. *N Engl J Med* 1988; 318:478-484.

Mathew CGP, Chin KS, Easton DF, et al. *Nature* 1987;328:527-528.

Simpson NE, Kidd KK, Goodfellow PJ, et al. *Nature* 1987;328: 528-530.

**Editor's comment**—The potential for malignancy of multiple endocrine neoplasia type 2A is frightening, but these new chromosomal and metabolic screening techniques allow us to recognize family members at risk. The screening techniques also suggest clear and reliable methods to be used in following at-risk individuals.

Judith G. Hall, M.D.

the thinness of the enamel and abnormalities of cusp formation. These dental abnormalities are unique to Morquio syndrome and are not found in any of the other mucopolysaccharidoses or spondyloepiphyseal dysplasias.

The authors studied the clinical and radiographic dental changes in 12 patients with MPS IV A and found varying degrees of the characteristic dental changes in all. These dental changes, however, are not present in either MPS IV B (beta-galactosidase deficiency) or MPS IV C (enzyme defect unknown). Although these dental abnormalities are present in all cases of MPS IV A, they may only be demonstrable radiologically in some clinically mild atypical cases. The dental changes are highly specific and can be extremely useful in the diagnosis of clinically atypical cases of MPS IV A.

## Clinical Findings in Twelve Patients with Mucopolysaccharidosis IV A (Morquio Syndrome): Further Evidence of Heterogeneity

### (I) Clinical and Biochemical Findings

Morquio syndrome has long been known as a distinct mucopolysaccharidosis (MPS) characterized by short trunk dwarfism with skeletal radiographic changes quite distinct from those of the other mucopolysaccharidoses, as well as corneal clouding, enamel dysplasia, and urinary excretion of keratin sulfate. In recent years, heterogeneity in Morquio syndrome has been delineated, with three main types described: MPS IV A, associated with N-acetylgalactosamine-6-sulfate sulfatase deficiency; MPS IV B, with beta-galactosidase deficiency; and MPS IV C, with mild manifestations in which the enzyme defect has not been determined.

The authors describe the clinical findings in 12 cases of MPS IV A and document markedly variable clinical presentations, with some cases only mildly affected. Nevertheless, all cases show deficiency of N-acetylgalactosamine-6-sulfate sulfatase in fibroblasts. The patients with the mildest clinical presentation showed a high residual enzyme activity, although several

had markedly diminished enzyme activity.

The urinary glycosaminoglycans (GAGs) were also examined in all patients by a two-dimensional electrophoresis technique that proved to be highly reliable and efficient. In particular, no false-negative results were obtained, which is often a problem with routine screening methods.

The authors divided MPS IV A into three subgroups: the severe "classical" type, an intermediate type, and a mild type, all caused by N-acetylgalactosamine-6-sulfate sulfatase deficiency. Residual enzyme activity may be an important prognostic indicator for each subgroup.

### (II) Dental Findings

Dental changes associated with Morquio syndrome have been recognized for some time. They are characterized by a thin enamel layer, with tooth surfaces marked by numerous, minute, irregularly distributed pits. The teeth, which are smaller than normal, are separated by spaces and the enamel appears to be structurally weak. Radiologic examination confirms

### (III) Odontoid Dysplasia

Spinal cord compression in the upper cervical region related to odontoid dysplasia is a major complication of Morquio syndrome. In addition to the odontoid hypoplasia, spinal cord compression is thought to be due to the associated ligamentous laxity and hypertrophy of the posterior longitudinal ligament. The pectus carinatum and sternal protrusion invariably found in these patients might act as a protective mechanism in some cases by limiting neck flexion.

The authors studied the cervical spine radiographically in 12 patients with Morquio syndrome; all showed evidence of odontoid dysplasia. In seven, it was defined as minor and in none of these was there evidence of instability. In five patients, the odontoid dysplasia was defined as major, with evidence of atlantoaxial instability in all five. The five patients with severe dysplasia and instability had classical Morquio syndrome, while the seven with minor dysplasia had milder atypical forms.

Long-term follow-up, with detailed neurological assessment, is essential in patients with Morquio syndrome. Any suggestion that the upper cervical cord is compromised by atlantoaxial instability should be investigated further by computerized tomography (with contrast dye) or by magnetic resonance imaging (MRI) so that the possibility of posterior fusion of the upper cervical spine can be considered in patients likely to benefit from this procedure. The degree of odontoid hypoplasia correlates well with the overall clinical severity of the condition, although the patients were of different ages when studied. Indeed, age-related variation in the dysplasia is another factor that must be taken into account.

Nelson J, Broadhead D, Mossman J. *Clin Genet* 1988;33:111.  
Nelson J, Kiniron S. *Clin Genet* 1988;33:121.

**Editor's comment**—These papers clearly demonstrate that, in addition to the known genetic heterogeneity in Morquio syndrome, there is significant clinical variability within individuals having the same enzyme deficiency state (*N*-acetylgalactosamine - 6 - sulfate sulfatase). These findings are similar to those that have been described in the other mucopolysaccharidoses: ie, in MPS I, deficiencies of alpha-1-iduronidase can be associated with typical Hurler syndrome, the very mild Sheie syndrome, or a variety of intermediate clinical states known as "compound heterozygotes"; the mild and severe forms of the Hunter syndrome associated with iduronate sulfate sulfatase deficiency; and the mild and severe forms of the Maroteaux-Lamy syndrome (MPS VI) associated with deficiency of arylsulphatase B. Thus, there appears to be both inter- and intramolecular heterogeneity in these disorders. Deficiencies of different enzymes due to mutations in different genes may produce similar clinical features:

ie, the San Filippo syndrome (MPS III A, B, C, and D) and Morquio syndrome (MPS IV A, B, and C). In contrast, different mutations along the same gene, resulting in variable deficiencies of the same enzyme, can produce marked clinical variability with severe and mild forms of the same phenotype.

The authors found that the enamel hypoplasia characteristic of Morquio syndrome is seen in all patients with MPS IV A, but is not present in MPS IV B or C. It therefore may be of diagnostic potential in cases of MPS IV, although in the mild forms of the disease, radiographs may be necessary to detect the enamel dysplasia. It is of interest that it is the enamel that is involved in Morquio syndrome, which is characterized by lysosomal vacuolization in epithelial-like cells. In osteogenesis imperfecta, where collagen is involved, it is the dentin that is abnormal.

Finally, the authors describe the variability in odontoid hypoplasia and atlantoaxial instability in pa-

tients with Morquio syndrome. Odontoid hypoplasia is characteristic of numerous skeletal dysplasias, including Morquio syndrome, the spondyloepiphyseal dysplasias, and metatropic dysplasia. Although it had been considered that all patients with Morquio syndrome have C1/C2 fusion of the spine because of the inevitability of atlantoaxial instability and spinal cord compression, the authors here demonstrate that in the mild forms of MPS IV A, there was no evidence of instability despite minor evidence of odontoid dysplasia. Nevertheless, all patients with Morquio syndrome must be followed longitudinally and with careful neurological and radiographic assessment of the C1/C2 area and cord. MRI, CT scanning, and neurophysiological studies should be done if there is any evidence of instability. If any evidence of spinal cord compression exists, fusion of the cervical spine is mandatory.

David L. Rimoin, M.D., Ph.D.

### Genomic Imprinting—Genes Inherited From the Father May Act Differently Than the Same Genes When Inherited From the Mother: Four Reports

Research on embryogenesis in the mouse, utilizing transplantation and transgenic mice, indicates that maternally derived genes seem to play a greater role in the early development of the embryo, while paternally derived genes play a greater role in the development of the extraembryonic membranes. The pattern of DNA methylation is different and depends on whether the alleles on the mouse chromosomes are maternally or paternally derived. These observations have been interpreted to suggest that differential imprinting of the genome occurs during male and female gametogenesis. These

findings may help to explain why human diseases such as myotonic dystrophy and Huntington disease, both autosomal dominant disorders, may vary in severity depending on which parent passed on the gene.

Marx JL. *Science* 1988;239:352-353.  
Solter D. *Trends in Genetics* 1987;3:23-27.  
Reik W, Collick A, Norris ML, et al. *Nature* 1987;328:248-251.  
Sapienza C, Peterson AC, Rossant J, et al. *Nature* 1987;328:251-254.

**Editor's comment**—This new work is startling, but "imprinting" has been observed by several groups. This suggests there are many such mechanisms at work in embryogenesis and early development that may be critical to normal growth.

Judith G. Hall, M.D.

## Chronic Intermittent Elemental Diet Improves Growth in Children With Crohn's Disease

Inadequate caloric intake over a prolonged period of time is considered the major cause of growth failure in children with Crohn's disease. However, appropriate nutritional therapy may reverse growth retardation and may even improve the clinical status of children with the disease. Seven boys and one girl, ages 9.8 to 14.2 years, with Crohn's disease and growth failure, were evaluated for a period of one year while receiving standard medical therapy. During the second year of the study, these children were given continuous feedings of an elemental diet (Vivonex) at night by nasogastric tube. These feedings were given for one month every four months for a total of three months of nutritional therapy. Four children, matched for age and disease, received standard medical therapy throughout the two years of the study. The parameters measured in all children were height, weight, triceps skinfold and mid-arm circumference measurements, Tanner stage of sexual development, the Crohn's disease activity index (CDAI), bone age, and prednisone intake. Hemoglobin, lymphocytes, serum albumin, iron, total iron-binding capacity, folic acid, and urinary creatinine were also evaluated.

Children receiving the intermittent elemental diet showed an increased annual mean growth velocity of  $7.0 \pm 0.8$  cm, as compared with their previous growth velocity of  $2.9 \pm 0.4$  cm. During the same period, children in the control group had a growth velocity of  $1.7 \pm 0.8$  cm ( $P < 0.01$ ). Significantly, patients treated with the elemental diet had greater weight gains, increased triceps skinfold thickness and arm muscle circumference, and increased creatinine excretion. In addition, the CDAI and prednisone

intake were reduced during the year of elemental diet feedings, compared with levels during the year of standard therapy and in the control group ( $P < 0.001$ ). However, no differences were noted in the advancement of bone age and pubertal development and in other biochemical and nutritional parameters between the groups.

Belli DC, Seidman L, Bouthiller AM, et al. *Gastroenterology* 1988; 94:603-610.

**Editor's comment**—This well-designed study provides further evidence that nutritional rehabilitation of children with Crohn's disease may reverse growth retardation and promote clinical improvement. In particular, it showed that intermittent elemental enteral feedings, given for one month out of every four months for one year, are sufficient to triple the growth rate. The mechanisms whereby elemental enteral feedings improved growth go beyond the provision of calories. The enteral feedings not only provided calories, but all necessary nutrients, while eliminating all other food intake. Additionally, children received supplemental vitamin K, folic acid, and more importantly, elemental iron. Any one or all of these nutrients could have contributed to the improved growth.

The effect of "bowel rest" while the children receive infusions of monomeric enteral feedings also may have played a role in reducing the antigen load and decreasing the disease activity. This may have reduced steroid needs, thereby allowing for more growth. The lessening of the inflammatory intestinal process may have also resulted in decreased energy needs by reducing the hypermetabolic effects of the diseased bowel and by alleviating anorexia. Whatever the mechanism, nutritional rehabilitation of Crohn's disease patients is essential, and should be attempted even before growth failure occurs.

The nutritional dwarfing of children with Crohn's disease is evident, even though they appear well adapted to decreased nutrient intake. Often, dietary intake is not reduced below the level needed to maintain body weight and height, but is insufficient for normal growth. Only stable isotope measurements may detect malnutrition in well-adapted Crohn's disease patients whose growth has slowed as an adaptive response to decreased nutrient availability. Treatment must include provision of all the necessary nutrients for growth, with surgery contemplated only if appropriate nutritional therapy fails.

Fima Lifshitz, M.D.

## Growth of Immigrant Children in the Newcomer Schools of San Francisco

This study evaluated the effects of migration and nutritional change on the heights and growth velocities of four groups of immigrant children (Chinese, Filipino, Hispanic, Southeast Asian) who were 5 to 12 years of age when they enrolled in one of three San Francisco schools. A low score on an English-language achievement test was the criterion for study entry. Education regarding nutrition was provided during the study.

At the initial examination, all four groups had mean heights and weights between the fifth and 25th percentiles, as calculated by United States reference population growth curves. In general, the Hispanic and Filipino children were above the mean when weight was compared to height ( $>50\%$  of children exceeded the mean), and the majority of the Chinese and Southeast Asian children were underweight for their height. During 12 months of observation, the children in all groups showed catch-up growth, with the growth velocities being above the 50th

percentile of the Fels longitudinal growth velocity curves for U.S. children.

The authors concluded that the catch-up growth indicated a growth deficit as a direct consequence of their previous environment and that they were malnourished (see editor's comment). The authors also noted that interpreting these data was difficult because they knew little about these children prior to their arrival in the U.S. For example, many of the Southeast Asian children had been in refugee camps where they may have received only minimal food and medical care.

Schumacher LB, Pawson IG, Kretchmer N. *Pediatrics* 1987; 80:861-868.

**Editor's comment**—Readers are strongly encouraged to read the article entitled "Malnutrition: Definition, Incidence, and Effect on Growth" by Dr. David Seckler (Growth, Genetics, and Hormones, Volume 1, Number 2). After reading Dr. Seckler's article, readers may question, as I do, whether the conclusion of Schumacher et al that these immigrant children were malnourished is necessarily correct. Dr. Seckler suggests that children grow in accordance with their nutritional intake, but that bigger is not necessarily better. The implications of Seckler's article may have gone unnoticed by many. If so, that is unfortunate since that article is extremely pertinent to our concepts of growth and nutrition.

Schumacher et al may be right in concluding that malnutrition was responsible for the short stature of the patients evaluated in their study, but if so, the malnutrition had to be one that was related to a specific factor or factors and not to calories alone, since the Hispanic and Filipino children were overweight for height. The Hispanic and Filipino population negated that consideration.

Robert M. Blizzard, M.D.

## A Wide Variety of Different Mutations of Collagen Seem to Be Responsible for Most Cases of Osteogenesis Imperfecta

Collagen is responsible for much of the strength of connective tissue. It consists of a triple helix of polypeptides, each with repeating segments of amino acids, with every third amino acid being a glycine molecule. The three polypeptides are tightly wound together, and glycine occupies the axial position. Thus, when mutations occur at a glycine site, the molecule is greatly weakened. Each collagen molecule (more than ten have been described) may be constructed of the same or combinations of different polypeptides.

Most cases of osteogenesis imperfecta (OI) are associated with mutations in type I collagen. Clinical effects depend on the particular position and domain of the collagen molecules in which a mutation or substitution occurs;

the closer the mutation occurs to the carboxyl terminus of the polypeptide of type I collagen, the more severe the clinical defect. Specific mutations have been identified in most cases of the lethal type of OI and for many non-lethal types. Each family has a distinct mutation that is different from mutations found in other families. Identification of a specific alteration or mutation can be used to recognize carriers in a particular family and to assist in prenatal diagnosis.

Sykes B. *Nature* 1987;330: 607-608.

**Editor's comment**—OI, a relatively common bone disorder that leads to short stature and multiple fractures in most cases, has several clinical subtypes. Recent research on collagen demonstrates the molecular basis for the disease and allows prenatal diagnosis. Recently, Byers brilliantly reviewed the subject of OI in this publication (vol. 4, no. 2). Readers are encouraged to read Dr. Byers' article.

Judith G. Hall, M.D.

## Prenatal Diagnosis of Congenital Adrenal Hyperplasia

The use of a combination of DNA probes for polymorphisms both within the 21-hydroxylase gene and in and around the closely linked HLA region permits reliable prenatal diagnosis of 21-hydroxylase deficiency in more than 95% of families at risk for having a child with congenital adrenal hyperplasia. Chorionic villus sampling during the first trimester permits early detection of the defect, and also provides the option of using intrauterine therapy in families where there is severe salt loss and significant masculinization of females.

Since masculinization is likely to have occurred prior to the prenatal diagnostic procedure, the current

recommendation is to treat the mother with dexamethasone as soon as the first menstrual cycle is missed. Treatment is continued until the results of chorionic villus sampling determine whether the fetus is male or female and whether it is affected or not. If the fetus is female and affected, treatment is continued throughout pregnancy.

Dreno B, Meignier M, Bignon JD, et al. *Lancet* 1987;ii:1272-1273.

**Editor's comment**—Although many families will opt for prenatal treatment of 21-hydroxylase deficiency, others will opt for termination of affected pregnancies. The new linkage techniques allow accurate detection and, therefore, offer more options to family and physicians.

Judith G. Hall, M.D.

## Increase of Serum Lipids and Serum Lipoproteins in Girls on Therapy With Estrogen and Norethisterone for Height Reduction

Weninger et al measured the levels of serum cholesterol and triglycerides in 23 tall girls, ages 11.2 to 15.5 years (mean  $12.7 \pm 1.1$ ) whose height was 2 to 4.2 standard deviation scores above the mean for age, prior to and during therapy with a combination of ethinyl estradiol (0.5 mg/day orally) and norethisterone (10 mg/day on days 21 to 25). These patients were followed for 11 to 24 months.

Serum cholesterol and triglyceride levels rose significantly (cholesterol,  $4.27 \pm 0.93$  mmol/L v  $5.33 \pm 0.65$ ,  $P < 0.001$ ; triglyceride,  $0.95 \pm 0.28$  mmol/L v  $1.82 \pm 0.57$ ,  $P < 0.001$ ) after three months of therapy. In a subgroup of 11 girls, low-density and high-density lipoprotein levels were determined; both rose significantly above baseline values after three months of treatment.

These investigators also evaluated the effect of norethisterone on the serum cholesterol and triglyceride concentrations immediately before and after five days of administration. No immediate effects of norethisterone were evident. After the cessation of all therapy, elevated lipid levels returned to pretreatment levels within 3 to 12 months in all but two patients.

The authors point out that the observed increase in lipids and lipoproteins during therapy for tall stature is in contrast to the physiological decrease in lipids that occurs during adolescence. Therefore, they conclude that therapy rather than sexual maturation is responsible for the lipid and lipoprotein changes they observed.

Weninger M, Frisch H, Schober E, et al. *Acta Paediatr Scand* 1987; 76:500-503.

## Pubertal Development in Male Hypopituitarism

In hypopituitary adolescents, puberty takes a different course than it does in normal individuals, patients with hypogonadotropic hypogonadism, and those with isolated growth hormone deficiency (IGHD).

Martinez et al analyzed the course of sexual maturation in 65 male patients with hypopituitarism who were treated at the Hospital de Niños in Buenos Aires between 1965 and 1982. Eighty-two percent of the children with IGHD and 32.5% of those with multiple pituitary hormone deficiencies (MPHD) experienced spontaneous puberty. Thirty-six patients

were followed longitudinally. Fifteen showed spontaneous sexual development commencing at a chronological age (CA) of 15 years, 3.2 years later than in normal Argentinian boys. Mean bone age (BA) was 10.4 years. There was no difference in BA between patients with IGHD and MPHD. Plasma testosterone was slightly but not significantly higher in these patients than in the controls.

Eleven of the 15 patients received human growth hormone (hGH) continuously; four could not be treated. Peak height velocity was  $7.49 \pm 1.7$  cm/year in the treated subjects and  $6.67 \pm 2.3$  cm/year in the untreated ones. Mean CA of the 21 subjects with MPHD whose sexual maturation

**Editor's comment**—Treatment of tall stature with estrogen has been used for several decades. Usually, the therapy is reserved for girls who are experiencing significant psychological problems because of tall stature. It has been stated that the earlier treatment is begun, the greater the reduction in adult stature. It has been well documented that height reduction can be achieved. However, there are numerous side effects associated with treatment. Do the benefits of treatment justify the risks?

Weninger et al have observed a marked increase in serum lipids and lipoproteins during combined estrogen and norethisterone treatment for height reduction in tall girls. Although this increase is transient, reverting to pretreatment values once therapy is concluded, the long-term effects of elevated lipids cannot be known at this time. Pediatric endocrinologists are cautioned that hormonal therapy for height reduction in tall girls may not be without significant risk and should be reserved for patients for whom counseling is not effective. The side effects described here should be discussed with the parents before initiating therapy.

William L. Clarke, M.D.

## Long-Term Monitoring of Treatment With r-hGH by Serial Determinations of Type III Procollagen-Related Antigens in Serum

The measurement of type III procollagen (P-III-NP) by two radioimmunoassays before and during treatment with human growth hormone (hGH) in 20 patients with GH deficiency was reported. One assay (RIAGnost assay) recognized the intact propeptide predominantly. The second (FAB assay) recognized both the intact propeptide and a smaller monomeric peptide.

In childhood, P-III-NP levels vary with age and correlate significantly with the growth velocity curves. In the 20 GH-deficient patients studied by the authors, P-III-NP and somatomedin-C (Sm-C) levels increased after three days of recombinant hGH (r-hGH) therapy (2 IU/m<sup>2</sup>, six or seven days per week). The values increased within one month to those usually seen in healthy children, but Sm-C levels did not increase above the values seen at three days.

Only two parameters—lower

was induced by gonadotropin was  $19.04 \pm 2.2$  years at start of treatment, while BA was  $12.94 \pm 0.8$  years. Plasma testosterone reached physiological values quickly, except in two patients who showed no response. Mean growth velocity of the patients who simultaneously received treatment with hGH was 6.11 cm/year and only 4.91 cm/year in those who did not receive hGH.

Martinez AS, Heinrich JJ, Rivarola MA, Bergadá C. *Eur J Pediatr* 1986;145:384-388.

**Editor's comment**—The observations confirm the often-published experience that the less global the central lesion is, the more

frequently spontaneous puberty occurs. The retardation of spontaneous puberty in the non-hypogonadotropic patients amounted to 3.2 years over healthy Argentinian boys. BA, however, corresponded to the standard of normal boys at start of puberty. Growth velocity was within the normal range in these boys. However, the observation that patients who did not receive GH also had high growth velocities appears to be remarkable. Their mean height velocity amounted to 6.67 cm/year, a value slightly but not significantly below that of the hGH-treated boys. For patients with GH deficiency, this value is surprisingly high.

Jürgen R. Bierich, M.D.

skeletal age and higher basal P-III-NP values as determined by the RIAgnost assay—studied during the pretreatment period proved to be associated with height increase after six months of therapy. Both seemed to have predictive relevance to growth velocity. Levels of basal Sm-C, alkaline phosphatase, or P-III-NP (by FAB assay) did not have predictive relevance for growth velocity during this period. The increases of P-III-NP levels following three days or one month of GH treatment did not correlate with the increase observed in growth velocity during the six months of treatment.

P-III-NP serum antigens measured by both assays correlate with each other but provide different information. The RIAgnost method recognized intact propeptide and may be more sensitive than the FAB assay in reflecting unstimulated basal collagen metabolism. The authors postulate that the correlation between the normal P-III-NP values obtained by the RIAgnost assay before treatment and the subsequent growth response indicates that reasonable normal collagen synthesis may be a prerequisite for a satisfactory growth response to

hGH. The authors further postulate that this is important because hGH is proposed as possible therapy for diseases in which disturbances of connective tissue or bone metabolism are suspected, such as in Turner syndrome. In patients with Turner syndrome, low basal levels of P-III-NP are reported, and the growth response to hGH is not as striking as that observed in patients with GH deficiency.

Danne T, Gruters A, Schnabel K, et al. *Pediatr Res* 1988;23:167.

**Editor's comment**—A marker to determine the propensity of various patients to grow well when hGH is administered is very much needed. A better understanding of the roles of various types of collagen in the growth process and their controlling factors, such as hGH, is also much needed. Danne et al have the methodology that permits them to begin the study of such phenomena. The importance of this article remains unknown, but it is presented because of its potential therapeutic implications and its succinct review of what is currently known about the effect of hGH on collagen synthesis.

Robert M. Blizzard, M.D.

## Growth of 519 Small-for-Gestational-Age Infants During the First Two Years of Life

Tenovuo et al have carefully followed the physical growth of 519 small-for-gestational-age (SGA) infants for a period of two years. SGA infants were defined as those below the tenth percentile on growth curves generated at the authors' institution. These infants were compared to 4,517 term infants whose length and weight were appropriate for gestational age. The authors used the Rohrer's Ponderal Index (PI)

$$\frac{\text{weight (g)}}{\text{length}^3(\text{cm})} \times 100$$

to classify the SGA infants.

Infants who were small with respect to weight and length (Type I intrauterine growth retardation [IUGR]) tended to have a normal PI, while those who were small with respect to weight only or who had disproportionate growth had a low PI. The latter infants have type II, or disproportionate, IUGR.

Approximately 92% of the SGA infants and 94% of the control infants took part in the follow-up study two years after birth. In addition to the comparison studies between the two groups, the authors utilized stepwise logistic regression analysis for determining variables, such as maternal smoking and toxemia, that might best explain the small neonatal size.

The findings demonstrate that SGA infants with a low PI were taller and had a larger head circumference at age 24 months than the term infants with a normal PI. Among preterm SGA infants, the degree of IUGR appeared to have no effect on later growth. The catch-up growth in SGA infants occurred in the first three months after birth although they remained significantly smaller than the control infants.

The type of IUGR affects later growth. Type II IUGR infants (PI

*continued on page 14*

### Growth of 519 SGA Infants *continued from page 13*

below the tenth percentile) grow better than type I SGA infants. In many cases, infants with type II IUGR have some nutritional deficit during the late stages of gestation and their growth potential is thus not permanently affected. Other studies have confirmed the finding that prolonged IUGR (which would result in a normal PI) is associated with poor growth in infancy. Later growth, however, could be predicted by the degree of weight retardation. By the age of 2 years, one in every four SGA infants, regardless of PI, still had a weight below the tenth percentile. The authors also demonstrated that the risk factors most often related to poor intrauterine growth are maternal toxemia, maternal smoking of more than ten cigarettes a day, multiple pregnancies, and the birth of a previous SGA infant. Unfortunately, these data were not analyzed with respect to the type of IUGR.

Tenovuo A, Kero P, Piekkala P et al. *Acta Paediatr Scand* 1987;76:636.

**Editor's comment**—*Although the article describing this study is somewhat difficult to read, the information presented is significant. The study demonstrates the difference between prolonged and short-term IUGR on future growth. Similar studies of infants from different populations should be carried out to confirm these findings. In addition, long-term follow-up studies of childhood growth and final adult height in these infants are required to provide better predictive information for pediatricians who counsel parents concerning their child's growth, and to help design studies directed at increasing our knowledge about growth reduction in these children. Parents of SGA infants should be advised that these infants will most likely remain smaller than average throughout the first two years of life.*

William L. Clarke, M.D.

### Predictive Value of Minor Anomalies: Association With Major Malformations

The report is part of an ongoing study of congenital anomalies in white newborns. In this study, in which 4,305 babies were scored for 114 minor physical findings and for all major anomalies, these data confirm the previous hypothesis that infants with three or more minor anomalies are at increased risk of having a major anomaly. In this study, the risk for a major anomaly in the presence of multiple minor anomalies was only 20%; previous studies found a much higher incidence. Less than 4% (3.76%) of the 4,305 babies had a major malformation. Approximately five sixths of these major malformations were considered significant and required intervention; the remaining one sixth were

thought to require no special care or treatment. The 3.2% incidence of major malformations requiring intervention is higher than previously reported. With regard to minor anomalies, 28% of the babies studied had one such anomaly, 8% had two, and 3.1% had three or more.

Leppig KA, Werler MM, Cann CI, et al. *J Pediatr* 1987;110:531-537.

**Editor's comment**—*This study indicates that the presence of multiple minor anomalies is a good predictor of a major malformation and that children with minor anomalies should be studied more intensively. It also indicates that minor anomalies are very common in the general population and that the presence of one or two minor anomalies should not cause great distress for the parents or the physician.*

Judith G. Hall, M.D.

### Effects of Testosterone Therapy for Pubertal Delay

Wilson et al reviewed the charts of 50 adolescent boys treated with testosterone enanthate in oil to determine the long-term effect of testosterone therapy on growth and sexual development. Each boy received a total of four 200-mg injections, each given at three-week intervals. The authors also reviewed the charts of 38 adolescent boys who did not receive treatment.

Follow-up data were requested from subjects whose baseline visit was at least two years earlier. Nineteen (58%) of eligible treated subjects and 11 (52%) of eligible untreated subjects responded. A height Z score (the number of standard deviations away from the mean height for age) was calculated for each boy, and bone ages were obtained and read using the method of Greulich and Pyle. Adult height was predicted by a computer program based on the method of Bayley and Pinneau. The mean bone age delay, height Z score, average Tanner stage, predicted adult height, growth rate, serum testosterone, and somatomedin C concentrations, as well as midparental heights, were not significantly different between the treated and control groups.

Initial response to treatment at four months showed a significantly greater increase over baseline in the height Z score. At 12 months, however, only the mean increase in sexual maturation was significantly greater in the treated group. To minimize the statistically confounding effect of potential additional growth, data on final growth were obtained from subjects who were over 17 years of age. There was no significant difference in final absolute height Z scores between the treated and untreated groups, but the mean increase of final height Z scores from baseline was significantly greater among treated subjects because of dif-

ferences in the standard deviation of the final height Z scores between the two groups. Although not statistically significant, the actual mean height of the treated group was 4.9 cm greater than that of the untreated group. There was no significant correlation between baseline predicted adult heights and the actual heights at the time of the last visit. This study demonstrates that four courses of 200 mg testosterone enanthate at three-week intervals do not appear to compromise adult height in boys with delayed puberty.

Wilson DM, Kei J, Hintz R, et al. *Am J Dis Child* 1988;142:96-99.

**Editor's comment**—Although others have looked at the long-term effects of different androgen preparations, control populations with which to compare results are often not available. In addition, most other studies have utilized long-term (9- to 12-month) treatment regimens. Wilson et al also looked at patient satisfaction with therapy, and 95% of the treated subjects indicated that they believed the treatment had been helpful.

The authors correctly point out that patients who fail to show signs of pubertal regression a year after therapy should be carefully re-evaluated for hypogonadism. We have previously reviewed other reports in this publication (Vol. 3, No. 4 and Vol. 4, No. 2) of the long-term effects on height of testosterone injections for pubertal delay. The present study corroborates the findings of those studies and presents additional useful data for pediatric endocrinologists who treat this common problem.

William L. Clarke, M.D.

#### Letter to the Editor

I write in reference to "Catch-Up and Catch-Down Growth: A Review" by Dr. Tanner (*Growth, Genetics, and Hormones*, Volume 3, Number 4). I found the article provocative and enjoyable. I must say, though, that I do not like the term "catch-down growth" because it does not convey the appropriate meaning to students. The term seems to imply that the children get shorter and/or lose height potential, which of course is not the case.

The phenomenon is essentially another form of catch-up growth. Perhaps "catch-up growth, type II" would be a better term. What really happens is that height ages are trying to catch up with bone ages. When linear growth is abnormally stimulated, as by a virilizing disorder, and the disorder is then alleviated, the growth velocity drops for a while—but only for as long as it takes the height age to catch up to the bone age. Bone length tends to catch up with bone maturation. The result is restoration of height potential. Then normal growth resumes.

"Compensatory deceleration" is an accurate term for the phenomenon, but it does not convey the concept that the process is preserving rather than reducing height potential. Perhaps the term "catch-up growth, type II" better conveys this concept.

Robert L. Rosenfield, M.D.

Professor of Pediatrics and Medicine  
University of Chicago School of Medicine  
Chicago, Illinois

#### Dr. Tanner's reply

*I agree that "catch-down" growth is not a perfect term. In the formal setting, auxologists use the phrase "compensatory deceleration" or, preferably, "homeorrhetic deceleration." This expresses precisely what one is after; namely, a deceleration that restores the child to his programmed growth chart.*

*In the original paper on catch-up growth, Prader et al (1963) pointed out that this phenomenon was simply a special case of the principle of homeorrhesis described by Waddington in his classic book *The Strategy of the Genes* (London, 1957). Homeostasis is a well-known term and describes the tendency of an organism to return to a balanced position when pushed away from it. "Homeorrhesis" describes the same tendency, but in relation to an organism moving through time. Rhexis signifies flow as opposed to stasis.*

*I am not so sure that Dr. Rosenfield's explanation of the mechanism of homeorrhesis is correct in the general case. It is possible to advance both height growth and bone maturation, for example, by overfeeding (or even by providing a nice roomy uterus) and the stimulus is terminated when the animal slows down in both respects. We do not understand the mechanism of this at present, nor even whether the control is chiefly central or chiefly peripheral. There seems to be a size-for-age mismatch involved, and perhaps maturation-for-age and height-for-maturation mismatches as well.*

*I admit that the term "catch-down growth" has its disadvantages, but "catch-up growth, type II" sounds like a rare disease, probably with chromosomal deletion.*

#### Address for Correspondence

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## MEETING CALENDAR

**October 7-8** International Growth Hormone Symposium. Vienna, Austria. Contact: Dr. H. Frisch, Scientific Secretary, Universitäts Kinderklinik, Allgemeines Krankenhaus der Stadt Wien, Wahringer Gurtel 18-20, A-1090 Vienna, Austria

**October 15-20** 57th Annual Meeting of the American Academy of Pediatrics. San Francisco, California. Contact: American Academy of Pediatrics, 141 Northwest Point Boulevard, PO Box 927, Elk Grove Village, IL 60009 (800-433-9016, outside Illinois; 800-421-0589, in Illinois)

**October 27-31** 40th Postgraduate Assembly of The Endocrine Society. Franklin Plaza Hotel, Philadelphia, Pennsylvania. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

**November 30-December 2** 8th Annual Bristol-Myers Symposium on Nutrition Research: Enteropathy of Infantile Malnutrition, Diagnosis and Management. Children's Nutrition Research Center, Houston, Texas. Contact: Vicki L. Forgac or Lila K. Lerner, Office of Continuing Education, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030 (713-799-6020)

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# GROWTH

## Genetics & Hormones

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### The Role of Confined Chromosomal Mosaicism in Placental Function and Human Development

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Canada

Chromosomal mosaicism has long been recognized in clinical genetics practice as a cause of abnormal development. By definition, constitutional chromosomal mosaicism is the presence of two or more cell lines with different chromosomal complements in one individual. It has been described for both autosomes and sex chromosomes. Diagnosis of a mosaic chromosomal syndrome is usually based on the finding of both a normal diploid cell line and an aneuploid cell line in cultured lymphocytes and/or skin fibroblasts.

Mosaicism may originate in early embryonic development through nondisjunction, anaphase lag, or structural rearrangement. The resultant mosaic pattern in the conceptus depends on many factors, such as the number of blastomeres at the time of mutational event, the cell lineage affected by the mutational event, and cell selection based on the viability of mutant cells.

Only recently has the importance of the timing of the mutational event and the cell lineage involvement been realized, and this has led to the recognition of

two types of constitutional chromosomal mosaicism: (1) generalized, and (2) confined to the placenta or to the embryo (Figure 1).

#### Generalized Chromosomal Mosaicism

Generalized mosaicism originates from a mutational event in the first or second postzygotic division. All tissues of the conceptus are affected. This type of mosaicism has been described for most autosomal trisomies and for both monosomy and trisomy of the sex chromosomes. Study of mosaic trisomy 21 in children has shown that the selection against a trisomic cell line occurs in blood lymphocytes, but the ratio of trisomic to diploid cells remains the same in skin fibroblasts.<sup>1</sup> More severe selection is found in the Pallister-Killian syndrome, where aneuploid cells eventually disappear completely in peripheral blood but remain present in fibroblasts.<sup>2,3</sup> In other sporadic dysmorphic cases, in which mosaicism can only be detected in fibroblast cells and has never been documented in lymphocytes, the distinction between the evolution of generalized mosaicism and confined mosaicism within the embryo and fetus becomes difficult.<sup>4-6</sup>

#### Confined Constitutional Mosaicism

The existence of confined forms of constitutional mosaicism is less well known. It is the pattern of cell lineage differentiation during early embryonic development that supports confinement of mosaicism arising during cleavage and blastogenesis to either the placenta or the embryo/fetus. Significant confined *placental mosaicism* results from viable mutations occurring in trophoblast or extraembryonic mesoderm progenitor cells, while significant confined *embryonic mosaicism* originates after early implantation and initiation of development of the embryo proper from a designated small number of embryoblasts.<sup>7-9</sup> Only mosaicism confined to the placenta will be discussed in this article.

#### Confined Placental Mosaicism

Confined placental mosaicism (CPM), defined as a dichotomy between the chromosomal constitution of placental tissues (both cytotrophoblasts and villous stroma) and embryonic/fetal tissues, is usually detected on chorionic villus sampling (CVS) at 9-12 weeks of gestation.<sup>10,11</sup> Its existence has

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## The Role of Confined Chromosomal Mosaicism

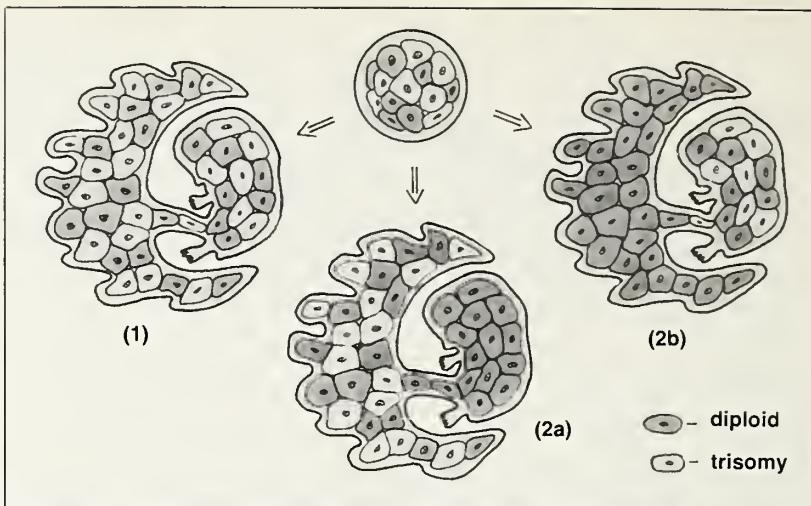
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also been demonstrated in term placentas.<sup>12,13</sup>

Discrepancies between the cytogenetic findings in cytotrophoblasts and villous stroma and fetus reported in 2% of pregnancies studied by CVS can assume three different forms, as shown in the table below.

Although such findings are designated in the current literature as CVS discrepancies or pseudomosaicism,<sup>11,14</sup> they exemplify constitutional mosaicism confined to the placenta.

The existence of CPM—with its expression restricted only to the cytotrophoblast, the extraembryonic mesoderm, or both of these lineages—and a complete absence of mosaicism in the embryo reflect the complexity of pre-implantation and early post-implantation placental development. Placental development starts at day 6 postfertilization when the implanting blastocyst invades the endometrium in the area of polar trophectoderm as two cell populations, cytotrophoblasts and syncytiotrophoblasts. These cells form primary villi between days 6 and 9, with the syncytiotrophoblast externally located and the cytotrophoblast internally situated (Figure 2). Secondary villi develop between days 9 and 18 by migration of the cells from both extraembryonic mesoderm and primitive embryonic streak into the villous core. Tertiary villi are characterized by the appearance of primitive capillaries in the villous core at about day 18.



**Figure 1** Diagrammatic representation of three types of constitutional chromosomal mosaicism: (1) generalized, (2a) that confined to the placenta, and (2b) that confined to the embryo.

After 3 weeks of development, chorionic villi have the structure of tertiary villi and are derived from three different cell lineages: polar trophectoderm, extraembryonic mesoderm, and primitive embryonic streak. Although both extraembryonic mesoderm and the embryo proper originate from the inner cell mass (ICM), it is possible that, in the case of mosaic blastocysts, the cells of the ICM that give rise to extraembryonic mesoderm may have a different karyotype from the cells migrating from the primitive streak of the embryo proper. The reason for this is that only a small number of cells (3 to 8) from the ICM become progenitors of the embryo proper.<sup>8</sup>

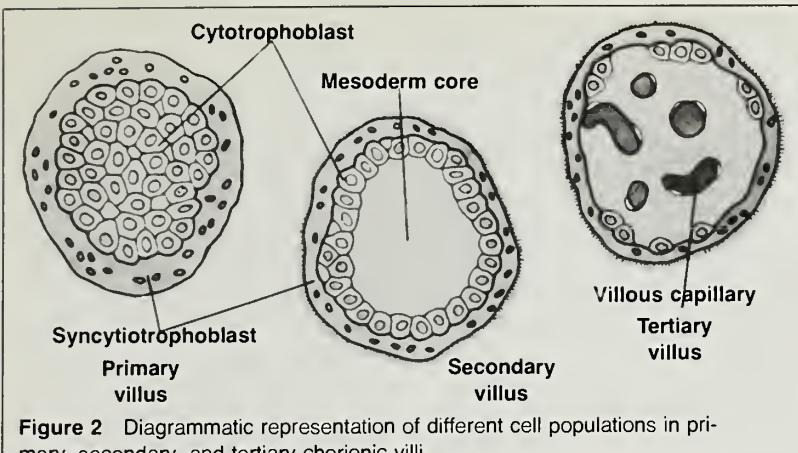
CPM can be understood by being aware of the complex embryonic derivation of placenta from three different lineages as well as by further development of the placenta. Cytotrophoblast, the cell

type utilized as a source of dividing cells in direct preparation of villi, is the predominant cell in primary placental villi and is an actively dividing cell in the secondary and young tertiary villi. However, by the fourth month of pregnancy, the cells of the cytotrophoblast become attenuated, lose their appearance as a continuous layer, and become difficult to demonstrate histologically. The existence of this cell type can be documented in term placentas by using special immunohistochemical techniques, but the cells appear inactive and sparse. Confirmation of the presence of an abnormal cell line in the cytotrophoblast that was identified at 10-12 weeks of gestation becomes technically more difficult at term, and it is not clear whether any selection against the aneuploid cell line takes place in mosaic placenta during the second and third trimesters, when the cytotrophoblast becomes less prominent.

All three cell lineages must be evaluated to study placental mosaicism. Trophectoderm lineage is analyzed by direct preparation or by short-term incubation of the chorionic villi.<sup>15,16</sup> Fibroblasts in long-term cultures of chorionic villi and chorionic plate represent the extraembryonic and embryonic mesoderm lineages. The derivation of amnion is still controversial.

**Table.** Discrepancies between the cytogenetic findings in cytotrophoblasts and villous stroma

Tissue	Type I	Type II	Type III
Cytotrophoblast	Mosaic or nonmosaic aneuploidy	Normal diploidy	Mosaic or nonmosaic diploidy
Placental stroma	Normal diploidy	Mosaic	Nonmosaic aneuploidy
Fetus	Normal diploidy	Normal diploidy	Nonmosaic aneuploidy



**Figure 2** Diagrammatic representation of different cell populations in primary, secondary, and tertiary chorionic villi.

### Role of CPM

Although the effects of CPM on placental function are not yet fully understood, some data documenting its significance exist.

Type I CPM is the most common. The aneuploid line in the cytotrophoblast detected on CVS has been shown to persist throughout the entire gestation in the same proportion (Kalousek DK, unpublished observation). It is not known why certain chromosomal trisomies (such as trisomies 3 and 15) occur frequently in type I CPM, while others are completely absent in this type.<sup>11,14</sup>

Although many pregnancies with this type of confined chromosomal mosaicism progress to term uneventfully and result in the birth of a normal live infant, some pregnancies result in unexplained intrauterine fetal death, intrauterine growth retardation (IUGR), or perinatal morbidity.<sup>16,17</sup> Abnormal placental function that interferes with fetal development may be the cause of pregnancies with complications. Not enough cases have been studied to make a correlation between a specific aneuploidy involved in mosaicism and pregnancy outcome.

Chromosomal mosaicism confined only to the chorionic villous stroma represents type II CPM. It is less common than mosaicism confined to the cytotrophoblast, and its effect on fetal intrauterine survival is largely unknown. It has been described in both normal pregnancies and pregnancies with fetal IUGR.<sup>12,13</sup>

In type III CPM, the presence of the diploid cell line confined to the cytotrophoblast in nonmosaic aneuploid conceptions appears to provide a protective effect and facilitate their intrauterine survival. It has been shown that all analyzed placentas from live newborns and terminated pregnancies with trisomies 13 and 18 were mosaic.<sup>19</sup> Prenatal diagnosis of this type of CPM by CVS is of concern, as it may lead to a false-negative diagnosis when only direct preparations are analyzed.<sup>10</sup>

### Role of CPM in Human Development

There are many unanswered questions regarding the effects of CPM on human development.

Although extensive information is available from studies of population cytogenetics data with respect to spontaneous abortuses, stillbirths, and live births, there are no data for their placentas. Although type III CPM facilitates intrauterine survival of embryos and fetuses with trisomies 13 and 18, the role of other types of CPM in the embryonic and fetal development is less clearly defined.

CPM has not been reported in spontaneously aborted conceptions, except for two cases involving type III mosaicism with the normal diploid cell line in the cytotrophoblasts and the tetraploid cell line in cultures of amnion, chorion, and villous stroma.<sup>17,18</sup>

It is obvious that further studies of placentas involving both direct preparations from trophoblast and

cultures from villous stroma, chorion, and amnion at different stages of intrauterine development are necessary to understand the chromosomal mutational events taking place during the cleavage and implantation period and the effect of these events on intrauterine development of both placenta and embryo/fetus. Studies at term that confirm the finding of CPM diagnosed by CVS are especially needed; only in confirmed cases can obstetrical findings such as IUGR or unexplained intrauterine fetal death be meaningfully associated with CPM.

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# Anabolic Steroid Hormones for Athletes: Efficacy or Fantasy?

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*Chief, Division of Pediatric Endocrinology and Metabolism*  
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Scientific interest in drugs is usually focused on their therapeutic effects—prevention, diagnosis, or treatment of disease—or on their abuse potential. Little attention has been given to the use of drugs for the following purported benefits: increase in physical strength, delay in the onset of fatigue, increase in exercise endurance, prevention of anxiety that could interfere with performance, enhanced attention and concentration, and development of a more satisfactory competitive attitude. The use of chemical or medicinal substances with the deliberate intention of altering athletic performance is generally considered unethical; for this reason, drug use by athletes is usually covert.

## Metabolic Actions

All anabolic steroids are derivatives of testosterone, the natural male sex steroid hormone that is responsible for the androgenic

and anabolic effects noted during adolescence and adulthood in males. Androgenic effects are those biologic activities that relate to the growth of the male reproductive tract and to the development of male secondary sexual characteristics. In the pubertal male, these effects are responsible for increases in the length and diameter of the penis, development of the prostate and scrotum, and the appearance of pubic, axillary, and facial hair. Anabolic effects are those occurring in the somatic or nonreproductive tract tissues, that is, those that promote nitrogen retention. Anabolic effects include an acceleration of linear growth before bony closure, enlargement of the vocal cords, the development of libido and sexual potentia, and an increase in muscle mass and strength.

During normal male pubertal development, testosterone is responsible for accelerated linear growth, in part by augmenting the amount of growth hormone secreted, increasing muscle bulk and strength, and decreasing the percentage of fat as body mass. This androgen is also probably responsible for the increase in aggressive and sexual behavior in

young males, although its role in these traits is controversial.

The androgens that produce predominantly anabolic (as opposed to androgenic) effects are esters of natural androgens or derivatives of 19-nortestosterone. Orally active agents are alkylated at the C-17 position of the androgen steroid nucleus. This chemical modification retards the hepatic metabolism of these agents. The parenterally effective compounds are mainly esters of the C-17 oxygen function and have an extended duration of action due to delayed systemic absorption from intramuscular sites. Methandriol is an exception, for it is a C-17 alkylated derivative. Oxandrolone is an anabolic steroid with a particularly favorable anabolic-to-androgenic activity ratio. In addition, there has been probably more experience with this compound than with any other for the appropriate stimulation of delayed growth in male and female adolescents, and girls with Turner syndrome.

The potencies and usual replacement dose ranges of many of the anabolic steroids taken by athletes in the United States are listed in the table below.<sup>1-3</sup>

**Table.** Anabolic steroid drugs

<b>Drug</b>	<b>Orally Active</b>		
	<b>Trade name</b>	<b>Relative potency</b>	<b>Usual dose range for replacement therapy</b>
Ethylestrenol	Maxibolin	≈ 8	4-8 mg/day
Methandrostenolone	Dianabol	≈ 2.5	5 mg/day
Oxandrolone	Anavar	13	5-10 mg/day
Oxymetholone	Anadrol-50	5-10	5-15 mg/day
Stanozolol	Winstrol	≈ 6	6 mg/day
<b>Parenterally Active</b>			
Nandrolone phenpropionate	Androlone	≈ 4	25-50 mg/week
	Durabolin		
	Nandrolin		
Nandrolone decanoate	Androlone D	≈ 3	50-100 mg, 3-4 × /week
	Deca-Durabolin		
Methandriol (also orally active)	Anabol	≈ 6	50-150 mg/day (oral)
	Durabolic		
	Methabolic		
	Methyldiol		
	Steribolic		

## Therapeutic Role

Anabolic steroids are medically unquestioned as replacement therapy in men with hypogonadism of central or peripheral origin and in some young males with marked delay of pubertal development. The amounts used, either orally or parenterally, are within severalfold of the normal male testosterone production rate. At these levels, normal pubertal progression and the maintenance of adult male strength and sexual function are attained, and untoward effects are usually minimal. Somewhat increased amounts are used to stimulate anabolism or to produce positive metabolic effects in some patients with neoplastic diseases. These agents may also be prescribed for patients with certain hormone-dependent tumors, such as breast cancer.

## Can Anabolic Steroids Improve Athletic Performance?

The most desirable effect of anabolic steroid use by athletes is an increase in muscle bulk, which is purported to give them more strength and power. One must realize, however, that objectively measured size and strength of muscle are not the sole determinants of athletic performance. Some athletes are very pragmatic and success oriented. Training methods that include the use of chemical compounds and drugs are chosen if the athlete thinks they will help. They may be needed

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merely for their placebo effect, or they may allow the athlete to train more diligently and/or more aggressively. The significant untoward effects (see following section) are most often quite removed in time from their use. As in any other clinical study, it would be important to follow athletes long term and to know precisely what agents were taken, how much, and for how long. Such data are unavailable at present and probably will always remain so because of the covert nature of most anabolic steroid use.

Although a large number of studies of the effects of anabolic steroids on athletic performance have been completed, there are very few that have been well controlled and randomized. Of those studies that have shown increases in muscle strength, virtually all evaluated highly trained athletes whose performance relied heavily on explosive muscular power to overcome the inertia of implements; for example, weight lifters or field event throwers.<sup>4</sup> The gains, based on relative increase in muscle strength, were small and statistically significant in less than half the studies. When evaluating relatively untrained subjects, it is very difficult to distinguish the results of training from those attributed to anabolic steroid use because of the very significant benefits of training itself. The aerobic performances of athletes treated with anabolic steroids do not exceed those expected from aerobic training itself.<sup>5</sup>

## Are Anabolic Steroids Harmful?

Some men taking anabolic steroids will experience prostatic hypertrophy, acne, and gynecomastia. At higher doses, they can expect more pronounced changes in these physical signs; priapism and edema are also common because steroids promote the retention of salt and water. This last effect explains, in part, the rapid weight gain that occurs after the administration of high doses of anabolic steroids and is probably the reason why

athletes taking these compounds can lose enormous amounts of weight very quickly after discontinuing these agents before certain competitions.

In women, anabolic steroids produce virilization, as indicated by enlargement of the clitoris, increased pubic, axillary and body hair, and libido. Menstrual dysfunction is common.

Abnormal hepatic function test results and mild jaundice are regularly seen in persons taking compounds that carry a 17-methyl (alkyl) group. Jaundice may also occur as a secondary phenomenon to other drug-induced liver diseases, such as peliosis hepatitis (the pooling of blood within the sinusoids) and/or hepatocellular carcinoma. More commonly, however, there is a lack of sperm production despite the heightened sexual drive in men receiving high doses of anabolic steroids. Although androgens are required for spermatogenesis, in high dosages they feed back upon the hypothalamus and pituitary to decrease concentrations of luteinizing hormone and follicle-stimulating hormone. The latter is an absolute requirement for the maturation of spermatozoa within the seminiferous tubules of the testes.

Some laboratory test results can be influenced by the levels of circulating androgenic hormones, and the results of certain tests—gonadotropin and thyroid hormone levels, for example—may become abnormal in persons taking anabolic/androgenic agents. Serum lipid levels correlate with the incidence of coronary artery disease—directly for total and low-density lipoprotein cholesterol (LDL-c) and inversely for high-density lipoprotein cholesterol (HDL-c). Anabolic steroids profoundly lower HDL-c levels, elevate LDL-c concentrations, and severely depress the HDL-c: LDL-c ratio. Thus, they are indirectly atherogenic.

The training regimens of body builders are often associated with a more favorable lipid profile than those used by power-lifters who are more likely to be in the cata-

*continued on page 6*

## Anabolic Steroid Hormones *continued from page 5*

bolic state after strenuous workouts. The different metabolic states may be important when attempting to verify drug activity.

Prepubertal and peripubertal children show disturbances in growth and sexual development, the most serious being the rapid advancement in bony epiphyseal closure. Children with diseases associated with androgen excess (eg, virilizing adrenal hyperplasia) are tall, muscular, and prematurely sexually developed as youngsters but relatively short as adults, since the maturational effects of the excessive hormones are potent. More profound actions are seen in men, and, by implication, in women and children who receive increasingly supraphysiologic doses of anabolic steroids. Great mood swings are common to those taking anabolic steroids, but frank psychosis, although reported a number of times, is quite rare.

Certainly, not all effects occur in all persons, nor are they necessarily obvious. In addition to the dosage, one must factor in the length of time that these compounds have been used to arrive at a total dose.<sup>6</sup> However, there have been a number of deaths

from hepatocellular carcinoma in young male weight lifters and body builders whose only risk factor was the long-term use of high doses of anabolic steroids.<sup>7,8</sup>

### Should Adolescent Athletes Take Anabolic Steroids?

The easiest recommendation to make is to say that no athlete should ever take these potent compounds for any reason. But as noted above, many athletes are supreme pragmatists who will not heed that advice, especially when faced with an immense amount of anecdotal information from their colleagues and competitors. Moreover, since many of the side effects have not occurred in the athlete or his/her companions who take anabolic steroids, there are only glowing stories of their efficacy. Many at this stage of life feel invincible, and have unrealistic views of dangerous practices.

Whether it is fair or allowable to take anabolic steroids before competition is a philosophical issue. In weight-related sports such as wrestling, the gain in weight might just put one into a higher weight class—not particularly advantageous unless one competed in the heaviest class.

I believe that the use of anabolic steroids ought to be condemned

except for therapeutic purposes. It is abundantly clear to me that prepubertal and peripubertal children of either sex should not have access to the anabolic/androgenic compounds because of their adverse side effects upon the growing and developing adolescent. Likewise, the potent androgenic effects of anabolic steroids upon the female reproductive system warrant their condemnation except in therapeutic situations. For the adult male competitor, I strongly feel that the potential side effects of these drugs far outweigh their purported benefits, and athletes should not use them.

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## Special Report: Seminar and Workshop on Limb Lengthening, May 23-24, 1988, San Francisco, California

Judith G. Hall, M.D.

*Associate Editor*

*Growth, Genetics, and Hormones*

This seminar was held to provide information to North American pediatric orthopedists on the remarkable new techniques that have been developed in Russia and Italy for lengthening of limbs. One section was devoted specifically to the lengthening of limbs in persons with disproportionate short stature. The history of leg lengthening and the techniques that have been used were reviewed. Professor Wagner from Germany discussed the Wagner technique, Professor Ilizarov from Russia described the Ilizarov

technique, and Professor DeBastiani from Italy described "calototasis" using the orthofix fixator.

A number of technical changes and improvements in leg lengthening in the past 5 years have led to lower complication rates and dramatically better results. The essence of the new lengthening procedure involves fixing a long bone (femur, humerus, tibia, fibula) at both ends by percutaneous pins or wires. An osteotomy is made midshaft. As the callus begins to form at the site of the osteotomy, the two ends of the bone are distracted from each other by the pins at the rate of about 1 mm/day. The newest research indicates that if that millimeter is divided into

fourths (ie, four smaller distractions a day) there is less pain and more rapid healing. The distraction process takes place over a 3- to 4-month period, after which the long bone is held in place to allow full strength and healing of the newly formed bone for another 4-month period (total, 8 months per limb segment). Patients are permitted to walk during the lengthening procedure. Most patients require only 5 or 6 days of hospitalization for the initial phase of the procedure, although weekly appointments for adjustments are required.

Leg-lengthening procedures should not be performed by those without experience or by those

who intend to do it on a one-time basis, since it is quite clear that many adjustments are required during the entire lengthening process. However, in the hands of experienced surgeons, patients can anticipate as much as 25 cm of increased length in a limb with two procedures (ie, femur and tibia). Use of the Ilizarov technique permits two osteotomies to be performed in the same limb segment, with two areas of lengthening.

Complications include stiffness of the joints, nerve palsy, skin infections, and very rarely, nonunion or fractures to the area of lengthening. Although minor adjustments and complications are frequent, the incidence of major complications appears to be less than 3% in experienced hands. Much higher complication rates

and much less lengthening were reported in earlier studies.

Limb lengthening is used not only for lengthening, but for non-union and pseudoarthroses as well. Although the technique was primarily developed for unilateral lengthening and for the treatment of amputations, it seems appropriate as a treatment for disproportionate short stature. It has been used in patients with hypochondroplasia and achondroplasia, but the results are much less promising in those with spondyloepiphyseal dysplasia. There are no reports of its use in those with other chondrodysplasias, although a few individuals with Turner syndrome and familial short stature have been treated in Europe.

Limb lengthening holds great

promise as symptomatic therapy for those with disproportionate short stature. At the same time lengthening is accomplished, bowing and other abnormalities can be treated. The ideal time for this treatment is adolescence so that the teenager with disproportionate short stature can have a growth spurt along with his or her peers. Moreover, by waiting until adolescence, the affected individual can participate in making the decision to undergo the procedure.

There is a great need for collaborative research to study carefully the outcomes of limb-lengthening procedures in different types of chondrodysplasias. Information about the long-term outcomes and complication rates of these procedures is simply not available at this time.

## Special Report: 48th Annual Meeting of the American Diabetes Association, June 12-14, 1988, New Orleans, Louisiana

William L. Clarke, M.D.

Associate Editor

*Growth, Genetics, and Hormones*

Although there were no presentations devoted specifically to growth in children with diabetes, there were several presentations on growth hormone (GH) pulsatility, insulin-like growth factor I (IGF-I), insulin resistance, and the relationship between GH and proliferative diabetic retinopathy that should be of interest to readers of this publication.

Cohen and Frohman (Cincinnati) characterized GH pulsatility in type I diabetic men. Utilizing both DETECT and PULSAR computer programming and 20-minute sampling for 24 hours before and after 10-14 days of improved glycemic control, they demonstrated an increased number of GH pulses (compared with controls) that did not change over the short term with improved glucose control. The diurnal rhythm of GH secretion was markedly abnormal in poorly controlled diabetics, with  $44 \pm 6\%$  of the pulses occurring between 8:00 A.M. and 8:00 P.M. After improved glucose

control, only  $26 \pm 4\%$  of pulses occurred during these hours.

The authors postulated that the time available for target tissues to recover from prior GH exposure is reduced in diabetics, particularly in those with poor glycemic control. They also postulated that these changes in GH secretory patterns may alter the nature of time-dependent GH metabolic effects in persons with diabetes.

Moxley et al (Rochester, New York) evaluated the effects of IGF-I infusions in adult rats using 2-hour euglycemic infusions. Measurements of 2-deoxyglucose uptake and hepatic glucose production were also performed. With infusion of low-dose IGF-I (21 U/kg/min), or high dose IGF-I (83 U/kg/min), whole body glucose disposal was similar to that seen when low and high doses of insulin were infused (2 mU/kg/min and 40 mU/kg/min, respectively). However, glucose disposal during the first hour of IGF-I infusion was significantly lower than that associated with insulin at each dose. At the low-dose infusion, IGF-I was less effective than insulin in suppressing hepatic glucose output. The authors con-

clude that IGF-I has insulin-like activity *in vivo* that results in part from crossover effects on the insulin receptor. They also demonstrated that IGF-I produces a fall in serum insulin. The physiologic significance of these findings is not clear.

Lager et al (Sweden) infused a tritiated glucose accompanied by either a placebo, propranolol, or somatostatin to evaluate glucose turnover following hypoglycemia. Hypoglycemia was shown to produce a prolonged insulin resistance (up to 7 hours). Propranolol did not prevent the insulin resistance, but somatostatin, which completely abolished GH release, significantly reduced this insulin resistance. The authors conclude that the late insulin resistance seen after hypoglycemia is not, like early-phase insulin resistance, due to  $\beta$ -adrenergic stimulation and that GH significantly contributes to this observation.

Two teams of investigators evaluated IGF-I and stimulated GH release in adults with proliferative diabetic retinopathy. Dills et al (Madison, Wisconsin) determined IGF-I levels in a large group of

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## Special Report: 48th Annual Meeting of the American Diabetes Association

*continued from page 7*

patients with diabetes. IGF-I levels were negatively correlated with age, duration of diabetes, and glycosylated hemoglobin, but were positively correlated with proteinuria. Using logistic regression analysis and controlling for duration of disease, glycosylated hemoglobin, blood pressure, and proteinuria, the authors demonstrated that higher levels of IGF-I

were significantly associated with an increased risk of proliferative diabetic retinopathy.

Janka et al (Boston) prospectively evaluated GH release to arginine in 91 insulin-dependent patients who had diabetes for more than 15 years and who had minimal background retinopathy. After 4 years of follow-up, those individuals who exhibited severe proliferative and preproliferative retinopathy had significantly higher postarginine GH responses. These differences remained after adjustments were made for hemo-

globin A<sub>1C</sub>, insulin dose, and creatinine. The study demonstrated, for the first time in a prospective manner, that individuals responding to arginine with high GH levels might be at risk for developing severe eye lesions.

The findings described by Dills et al and Janka et al differ from previous reports since it has been previously shown that high GH levels in persons with diabetes are usually associated with lower IGF-I levels. It should be noted, however, that Dills et al did not determine GH levels in their patients.

## Special Report: Fifth International Auxology Congress, July 20-23, 1988, Exeter, United Kingdom

Robert M. Blizzard, M.D.  
*Chairman, Editorial Board  
Growth, Genetics, and Hormones*

This excellent international conference on the measurement, physiology, and pathophysiology of growth was arranged by Dr. James Tanner. Its strength and interest evolved from the great diversity of the participants, who included economists, embryologists, statisticians, chemists, pediatricians, pediatric endocrinologists, and educators.

The roles of insulin-like growth factors (IGF) were discussed by Drs. Underwood, Froesch, and Hintz. The gene for IGF-I has five exons that have at least two ways to splice into two prepro hormone variants. The prepro IGF-I (E peptide) is present in large quantities in the plasma of patients with renal failure. In addition to the various prepro IGFs and two separate IGFs, there are several binding proteins that may act as storage receptacles for IGF-I, which itself has a very short half-life when in the unbound state.

Much emphasis is currently placed on investigating the role of IGF-I in various nutritional states. In human beings on restricted diets, IGF-I falls significantly. Restoration to previous levels is dependent on adequate caloric replacement and replacement of protein requirements with essen-

tial amino acids. In contrast, the use of nonessential amino acids limits the increase of IGF-I to prediet levels.

IGF-I infusion into growth-retarded diabetic rats leads to near-normalization of growth, as does IGF-I infusion in hypophysectomized rats.

Short-term measurements using knemometry were discussed by several investigators. Dr. Hermannusen (Kiel, West Germany) reported data based on extensive observations of patients and refined statistical methodology to study mini growth spurts. Seventy percent of healthy children were observed to have sharp growth spurts alternating with periods of decreased growth velocity, with a peak-to-peak distance of 30-55 days. He concluded that these mini growth spurts seem to be a major reason why the differences of leg lengths, which are obtained at short intervals, are inadequate for long-term growth prediction. Thus, the investigation of short-term growth, starting from the traditional idea of convertibility of length increment to growth, is complex, and the problem is far from being solved satisfactorily.

Since measurements of the tibia may be of use in studying the physiology of growth patterns in long bones and the spine, Dr. Cronk and associates (Philadelphia) designed a knemometer that

is smaller, more portable, and less expensive than the one previously designed by Dr. Valk. We may be hearing more concerning this type of bone study with the new machine if the limitations are understood and the equipment is truly less expensive.

Dr. Mosier (Irvine, California) presented data from studies of growth retardation and catch-up growth in infant rats following cranial irradiation or glucocorticoid administration. Mosier concludes that growth retardation and catch-up growth secondary to irradiation are under control of the central nervous system. The concept of central control requires that there be a mechanism for sensing current body size, a set point for target size (normal body size for age), and a means of stimulating increased growth rate. He believes that the set point is altered by radiation, and this change in set point is independent of nutritional or endocrine dysfunction as they can currently be assessed. The area of the dorsal medial hypothalamic nucleus is thought to be involved in the determination of the set point. However, all scientists interested in these phenomena realize that little is known as yet, and this difficult and important field of investigation needs extensive study.

The Sixth International Auxology Congress will be held in 1991 in Madrid, Spain.

## Three-Year Results of a Randomized Prospective Trial of Methionyl GH and Oxandrolone in Turner Syndrome

Seventy girls with Turner syndrome were divided into four groups to receive growth hormone (GH) (0.125 mg/kg, 3 times/week), oxandrolone (either 0.125 mg or 0.062 mg/kg daily), or a combination of both agents. Sixty-five subjects were evaluated after three years of therapy.

GH given alone over three years increased the growth velocity (GV) from  $-0.1$  standard deviations (SDs) on the Turner growth charts to  $+3.1$ ,  $+2.0$ , and  $+1.4$  SDs for the first, second, and third years, respectively. By the end of three years the mean height was  $+0.7$  SD, and five of 17 patients (29%) had heights above the 90th percentile. The increment in bone age over three years was  $2.73 \pm 0.72$  years. The  $\Delta$  Turner height age/  $\Delta$  bone age was 1.6 at the end of three years, and the  $\Delta$  predicted height was  $+4.5 \pm 0.9$  cm. After three years, four of 16 girls receiving GH alone achieved their projected adult height according to the Turner growth curves. All 16 were still growing at the end of the evaluation period. GV fell from a mean of 6.6 cm the first year of treatment to 5.4 and 4.6 cm during the second and third years, respectively. This compares to a value of 4.5 cm/year before therapy. The decrease in GV occurred although the insulin-like growth factor-I (IGF-I) values increased progressively over four years from 0.55 to 2.46 U/mL, indicating that the GV did not correlate over a long period of time with the IGF-I concentrations.

Combination therapy proved more effective than GH therapy alone. This was without apparent adverse effect on the rate of bone maturation or predicted adult height. The GV in this group increased from  $-0.1$  SD on the Turner growth charts to  $+6.6$ ,  $+4.3$ , and  $+1.4$  SDs for the first, second, and third years of treatment, respectively. By the end of

three years the mean height was  $+2.0$  SDs, and 11 of 16 patients (69%) had heights above the 90th percentile on the Turner growth curves. The increment in bone age over three years was  $4.0 \pm 1.2$  years. A  $\Delta$  Turner height age/  $\Delta$  bone age was 1.6 at the end of three years and the  $\Delta$  predicted height was  $+8.2 \pm 1.4$  cm for this group. After three years, ten of 16 girls receiving the combination therapy achieved their projected adult height according to the Turner growth curves, and all were still growing. GV fell from a mean of 9.8 cm during the first year of treatment to 7.4 and 6.1 cm for the second and third years, respectively. These compared to a pre-therapy value of 4.3 cm/year. As in the group on GH therapy, the IGF-I values increased with therapy but did not correlate with GV.

Oxandrolone was used alone in 17 patients and for only one year. The mean GV increased from 4.1 to 7.6 cm/year. Since these patients then received combination therapy, the prolonged effect of oxandrolone could not be evaluated, but previously published data indicate that GV in such patients return to the pretreatment rate during the third year of treatment. Oxandrolone used alone resulted in no significant increase in IGF-I values.

The GV data from the patients receiving GH alone compare favorably with those reported in three other studies. The effect of therapy on adult height is more

difficult to assess, but all 65 subjects who completed the study continue to grow. However, the median  $\Delta$  height age/  $\Delta$  bone age values suggest a permanent increase in predicted adult height since 65% of those receiving combination therapy have already equalled or exceeded their projected adult heights.

Appropriately, the authors point out that GH and oxandrolone are potent anabolic agents and are capable of causing insulin resistance, virilization, and the clinical stigmata of acromegaly. Also, patients with Turner syndrome do not respond to GH as well as GH-deficient patients, and the expectations of the patient, family, and physician for increased growth must be realistic. The authors also point out that it still remains to be seen whether such treatment will permit a significant number of these girls to attain a "normal" adult height of  $>150$  cm.

Rosenfeld RG, Hintz RL, Johanson AJ, et al. *J Pediatr* 1988;113:393.

**Editor's comment**—This editor has avoided treating patients with Turner syndrome with GH, but the current evidence suggests that we may eventually see an increase in ultimate height. If patients with Turner syndrome are to be treated, I certainly agree with the authors' comments that the expectations of the patients and parents for increased growth must be realistic.

Robert M. Blizzard, M.D.

### In Future Issues

The Morbid and Functional Anatomy of the Human Chromosome Map in Endocrine Disorders and Hormonal Genes by Victor A. McKusick, M.D.

Occult Celiac Disease: A Common Cause of Short Stature by Asaria Ashkenazi, M.D.

Growth, Sexual Precocity, and Treatment: Physiology and Pathophysiology

by Paul Boepple, M.D., and William Crowley, M.D.

## Immunoreactive Sm-C/IGF-I in Urine From Normal Subjects, Pituitary Dwarfs, and Acromegalics

The authors report the development of a somatomedin-C (Sm-C) radioimmunoassay that permits measurement of minuscule quantities of Sm-C found in urine (1/1000 the quantity/mL in serum). The assay was used to measure Sm-C in the early morning urines of three acromegalics, 15 growth hormone (GH)-deficient children, and 25 normal adults, and in the urines of 230 normal infants, children, and adolescents. The total excretion was referred to the creatinine excretion (Cr) to gain more consistency than was otherwise possible. The mean GH:Cr values for ten different age groups were:

Newborn	1-23 mo	2-3 yr	4-5 yr	6-7 yr	8-9 yr	10-11 yr
1.07	0.34	0.38	0.36	0.23	0.23	0.28
12-13 yr	14-16 yr	25-45 yr				
0.23	0.19	0.19				

Mean values of GH:Cr were high in the newborn (1.07) but much lower (0.34) in children 1 month of age or older. The values for the three acromegalics were 17.3, 1.52, and approximately 1.10. The values for the 15 children with GH deficiency (GHD) were all less than the mean for age, but only five were below -2 standard deviations for age. The test probably cannot be used for the diagnosis of GHD at this time.

The authors emphasize that no correlations have been made with serum GH concentrations or serum Sm-C determinations. The urinary concentrations of Sm-C are in most cases only 0.1-1 ng/mL,

much lower than one might have expected from plasma concentrations. The presence of binding proteins for Sm-C in plasma may contribute to the discrepancies observed between plasma concentrations and urinary excretion. It is possible that the Sm-C found in urine is secreted by the renal tubules. Further studies are needed to clarify the physiology involved.

Yokoya S, Suwa S, Maesaka H, et al. *Ped Res* 1988;23:151.

**Editor's comment**—Both Sm-C and GH are now measurable in very minuscule quantities in urine. The amounts of each are so small that it is difficult to believe that these assays will be pertinent to routine clinical studies. However, they may have applications in research. The reader is encouraged to read the abstract on page 15 on quantitation of urinary GH in children with normal and abnormal growth.

Robert M. Blizzard, M.D.

## A Triumph of Reverse Genetics: Characterization of Dystrophin in Duchenne and Becker Muscular Dystrophy

During the last five years, dramatic advances have been made in the study of Duchenne muscular dystrophy through DNA techniques in patients with visible X chromosome deletions or translocations through the Duchenne gene. It has been possible to isolate the gene and describe the protein (dystrophin) that is missing in Duchenne muscular dystrophy and abnormal in Becker muscular dystrophy. DNA analysis has demonstrated that these two diseases, which were thought to be separate, are in fact allelic.

The dystrophin gene, which is very large, has more than two million base pairs. The protein that has subsequently been isolated is also very large (400 kd) but it occurs in low amounts and repre-

sents only 0.002% of total muscle protein. The protein appears to be a subcellular component of the plasma-membrane system of normal muscle fibers. There are both qualitative alterations that lead to more severe muscular dystrophy and quantitative alterations that cause milder dystrophy.

It appears that at least one third of all cases of Duchenne muscular dystrophy represent new mutations, and at least half of them occur as deletions in or of the dystrophin gene. There still remains a great deal of work to be done in Duchenne muscular dystrophy. Defining the gene and the missing protein is only the beginning. Finding ways to treat affected individuals and replace the missing protein is the next step.

Hoffman EP, Fishbeck KH, Brown RH, et al. *N Engl J Med* 1988;318:1363-1368.

Rowland LP. *N Engl J Med* 1988;318:1392-1394.

**Editor's comment**—Research in molecular genetics is providing the information to work miracles, but the miracles begin with what can be found in the patients themselves. Patients with single-gene disorders who have visible cytogenetic alterations may well be the way to get to specific genes.

Judith G. Hall, M.D.

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## Long-Term Growth in Juvenile-Acquired Hypothyroidism: The Failure to Achieve Normal Adult Stature

Hypothyroidism was diagnosed and treated in 18 girls and six boys with a mean age of approximately 10.5 years and a mean bone age of 6.1 years. At diagnosis, heights were  $4.05 \pm 0.5$  standard deviations (SD) and  $3.15 \pm 0.5$  SD below the 50th percentile in girls and boys, respectively. Prior to deceleration of growth the mean height of all patients was less than  $\pm 0.3$  SD from the 50th percentile. The bone age at diagnosis closely matched the age at which deceleration of growth began, which suggests that the bone age at diagnosis corresponds well with the onset of severe hypothyroidism. L-thyroxine was given at  $3.4 \pm 0.3$   $\mu\text{g}/\text{kg}/\text{day}$  for treatment. Serial bone age determinations were available in most cases.

Mature heights were  $2.1 \pm 0.2$  SD below the 50th percentile. Differences between the predicted mature heights and the actual mature heights were  $7.7 \pm 6.0$  cm and  $6.7 \pm 5.5$  cm for females and males, respectively. The loss occurred primarily in the first 18 months of treatment and correlated significantly with the duration of hypothyroidism and the height SD at diagnosis. There was no correlation between the loss in mature height and the

chronologic, height, or bone ages at diagnosis.

The authors demonstrated that catch-up growth is incomplete after treatment of long-standing juvenile hypothyroidism. In brief, these patients rarely achieve their full genetic growth potential. The authors conclude that the possible etiologies for this deficit include: (1) overtreatment; (2) prolonged hypothyroidism, which diminishes the potential for catch-up growth; and (3) puberty coinciding with initiation of therapy, which results in completion of skeletal maturation prior to the completion of catch-up growth.

The thyroid function tests did not indicate overtreatment. Loss in predicted height during the first 18 months of treatment occurred in children who did not exhibit pubertal changes. The authors suggest that multiple factors may be involved but a delay in therapy is a critical factor in limiting catch-up growth that underscores the need for early recognition of hypothyroidism.

Rivkees SA, Bode HA, Crawford JD. *N Engl J Med* 1988;318: 599-602.

reach expected adult heights in patients with prolonged juvenile hypothyroidism has been apparent to most pediatric endocrinologists but data documenting its occurrence and extent have been lacking. Rivkees et al have provided us with those data, thereby permitting postulations that can be tested to be made. They are to be congratulated for their contribution.

The decision to be made now is what to do for the next patient with prolonged hypothyroidism so that he or she can achieve the height inherent in his or her genetic potential. I would use a lower dose of thyroxine than that used by the authors, as  $3 \mu\text{g}/\text{kg}/\text{day}$  in older children may be more than is necessary to attain a euthyroid state. Alternative approaches might include the use of an analogue of leutinizing-hormone-releasing hormone(a) to block puberty and/or the addition of growth hormone. These latter approaches, if chosen, should be used within rigid protocol guidelines and, therefore, should not be considered by most of us unless we are willing and able to establish and follow such a protocol.

### Editor's comment—Failure to

Robert M. Blizzard, M.D.

GnRH was administered subcutaneously in a pulsatile fashion via pump. Initially, GnRH was administered only at night to mimic the normal nocturnal pattern of gonadotropin secretion in early puberty. However, when girls attained breast stage 3 and boys attained a testicular volume of 8 mL, pulsatile GnRH was administered over the 24 hours of each day. The duration of treatment averaged 1.05 years in both boys and girls.

Serum GH levels were sampled every 15 minutes between 8 P.M. and 6 A.M. prior to the initiation of the study, at 1- to 3-month intervals throughout the study, and 1 month

after the cessation of treatment. GH profiles were analyzed using the PULSAR computer program. GH pulse frequency, the sum of the GH peaks, and the area under the GH pulses were calculated for each overnight GH profile, and then correlated with breast stage in girls and mean testicular volume in boys.

Twenty-four patients responded to pulsatile GnRH treatment with the normal sequence of sexual maturation. Peak growth velocity occurred between breast stages 2 and 3 in girls; GH secretion was increased at stage 2 but was significantly increased with its peak value at stage 3. GH secretion de-

## Mechanism of the Adolescent Growth Spurt Induced by Low-Dose Pulsatile GnRH Treatment

Stanhope et al studied growth velocity and growth hormone (GH) secretion in 14 females and 12 males with pubertal delay during treatment with gonadotropin-releasing hormone (GnRH). The findings were then related to stages of sexual development. All 26 patients in this study had puberty delayed by two standard deviations or had puberty arrested for at least 18 months. The mean ages were 16.4 years for girls and 16.8 years for boys.

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**Mechanism of the Adolescent Growth Spurt Induced by Low-Dose Pulsatile GnRH Treatment**  
*continued from page 11*

creased at the attainment of stage 4, after which it was altered cyclically depending on the stage of the menstrual cycle. There were no significant changes in GH pulse frequency.

In boys who responded to pulsatile GnRH treatment, there was an initial significant fall in the sum of GH peaks and in the area under the GH pulses with the onset of treatment, although testicular volume increased to 5-6 mL and virilization was initiated. A rapid increase in growth rate occurred at a testicular volume of 9-10 mL and reached a peak value between 11 and 15 mL. Peak height velocity (between 11 and 12 cm per year) coincided with peak GH secretion. The mean change in GH secretion demonstrated a pattern similar to the change in growth velocity. Se-

rum testosterone concentrations rose progressively throughout puberty, with no dramatic rise at the onset of the growth spurt.

Based on their study findings, the authors suggest that the mechanism of increased GH secretion is not due solely to sex steroid secretion, since testosterone secretion and virilization in boys occurs during early puberty while the growth rate and GH secretion continues to decelerate. They suggest that the level of testosterone achieved at a testicular volume of 10 mL may be important in the etiology of the increase and amplitude of the GH pulses. They also suggest that there may be an interaction between GnRH and somatotroph function.

Stanhope R, Pringle P, Brook C. *Clin Endocrinol* 1988;28:83-91.

**Editor's comment**—This study adds important information to the understanding of the mechanism

and timing of growth acceleration in puberty and the relationship to testicular volume and serum testosterone. Unfortunately, serum testosterone values are not reported in this paper. Others have demonstrated the relationship between testosterone and the increase in GH secretion and have demonstrated that testosterone increases mean GH secretion and the amplitude of GH pulses in prepubertal boys. The authors of this article have presented longitudinal data on a small group of patients, half of whom were later determined to have hypogonadotropic hypogonadism and half to have constitutional delay of puberty. They correctly point out that there are no longitudinal data available on physiologic GH secretion during normal puberty with which to compare their findings. Such studies should shed further light upon the mechanism of growth acceleration during puberty.

William L. Clarke, M.D.

**Diagnosis of GH Deficiency and GH Treatment**

The availability of recombinant growth hormone (GH) has directed much attention to the diagnosis and treatment of GH deficiency (GHD). Rose et al of the NIH recently published in the *New England Journal of Medicine* an extensive analysis comparing the use of pharmacologically stimulated GH levels with spontaneous GH secretion—as determined by the GH levels over 24 hours—to diagnose GHD.

Three pharmacologic stimuli were used in 54 children with severe short stature. In 23, all GH values were  $\leq 7$  ng/mL, and these children were classified as GH-deficient on this basis. These results were compared with the mean integrated GH concentrations (ICGH). All 31 children who responded to pharmacologic tests with values  $> 7$  ng/mL had ICGH

values in the range found in 46 normal-statured prepubertal children. Therefore, the authors conclude that no additional patients with GHD were detected and that the timely and costly measurement of ICGH in short children is of little diagnostic value.

The correlation between the results of the pharmacologic tests and ICGH levels in the GHD patients was poor, as only 57% of the 23 patients had ICGH levels below the range found in the 46 controls. Therefore, the authors recommend that the use of pharmacologic stimuli is sufficient to diagnose GHD.

The authors explain that the inclusion of more appropriate control subjects accounts for the discrepancy between their studies of ICGH with those of others. They postulate that the 43% of children with GHD, who had ICGH levels in the lower 20% of normal range, were children who require a higher GH level than most to grow nor-

mally; some defect reduced the spontaneous secretion of GH until it was in the lower normal range, and the defect was revealed after pharmacologic testing. Rose et al readily point out that further studies are indicated to determine how to best diagnose GHD.

They also report that the ICGH levels in the 46 controls did not correlate significantly with age, sex, height, weight, insulin-like growth factor (IGF-I) level, or growth velocity for age, although the IGF-I levels in the 31 short children without GHD were between the values seen in controls and GHD children.

In an editorial in the same journal, Grumbach addressed the use of GH therapy in GHD and short stature. He states that the criteria of Rose et al for the selection of short children for treatment with GH was rigidly defined and straightforward.

In the past, treatment was restricted to children with growth

velocities below the 25th percentile for age and GH levels  $\leq 14$  ng/mL on at least two provocative tests. However, conventional tests to define GHD have important limitations, including a paucity of standards that are related to age and sex in normal children. Also, there is growing concern about the variation in GH concentrations when kits from various commercial suppliers are used to measure GH levels.

Grumbach agrees that the observations of Rose et al are important and have practical implications. He agrees that the 24-hour GH profile remains a useful research tool but probably should not be used as a routine diagnostic procedure or in the selection of children with idiopathic short stature (ISS) for trial therapy with GH. He emphasizes that not one of the tests of GH secretion is, in fact, a useful discriminant in the selection of short healthy children for a trial therapy with GH. After excluding frank GHD by provocative tests, one acceptable approach is to categorize children with ISS as either responsive or unresponsive to GH over a 6-month period of treatment. This raises a most important question: Will the treatment increase the predicted height or merely lead to the attainment of adult height at an earlier age?

Ethical and economic issues must also be considered. For example, how will abuse of GH be avoided? Grumbach emphasizes that long-term, well-controlled studies to resolve the issues must be done promptly. He draws attention to the usefulness of oxandrolone, low-dose estrogen, and low-dose testosterone, all of which can be used as alternate therapeutic agents in certain short children (eg, those with constitutional delay of growth and Turner syndrome). His astute conclusion is that in considering GH treatment in children with ISS, we should recognize that the problem lies not in the GH profiles, but in the role of "heightism" in our society and the

psychosocial disadvantage it confers.

Rose SR, Ross JL, Uriarte M, et al. *N Engl J Med* 1988;319:201.

**Editor's comment**—Whoever says that life and the practice of medicine are easy has not visited the offices of doctors who treat short children. Although all agree that GHD is present in the patient with no response above 5 ng/mL (as determined by the GH assay utilizing the reagents and standards of the National Hormone Pituitary Agency), there are other short children who have partial GHD who will not be diagnosed in 1988 by pharmacological stimuli that test for GH adequacy. As pointed out by Reiter et al (J Clin Endocrinol Metab 1988;66:68), the results of GH concentrations vary widely with different assays. In our laboratory, the same serum specimen will yield a value of 4.0 ng/mL by the Hybritech assay and 8-12 ng/mL by the Nichols' kit assay. Some clinics using the same assay consider abnormal only values  $\leq 7$  ng/mL in response to a pharmacologic test; other clinics classify only values  $\leq 14$  ng/mL as abnormal. In addition, some of the short children with "normal" test results by accepted pharmacologic testing criteria will have low IGF-I concentrations and/or markedly delayed bone ages and/or low or low-normal ICGH levels. These patients may have GH inadequacy,

but not necessarily GHD, if GHD is interpreted as decreased GH production. GH inadequacy can encompass the production of a biologically inactive but immunologically active hormone or a partial resistance in generating IGF-I, which might be overcome with increased exposure to GH. The latter is comparable in concept to vitamin D dependency, a condition in which pharmacologic amounts of vitamin D are required to produce normal amounts of 1 $\alpha$ 25 dihydroxycholecalciferol.

Are these very short patients with possible GHD or inadequacy, whose physicians cannot agree on a uniform level of GH for interpretation of normalcy or on the GH assay to be used, to be deprived of GH? Rose et al and Grumbach have written that "further elucidation of what comprises GHD (and inadequacy) will need to be clarified, and the long-term effect of GH on ultimate height in ISS will have to be determined." In my opinion, a humane approach permits the occasional prescribing of GH on a trial basis for children with extreme short stature with possible deficiency of GH or inadequacy. However, all of us must prescribe judiciously to prevent abuse of GH. Most importantly we must be sympathetic, considerate, and supportive of those who are affected by the "heightism" in our culture.

Robert M. Blizzard, M.D.

## Body Composition of Peruvian Children With Short Stature and High Weight for Height

Chronic undernutrition frequently occurs among children from underdeveloped countries. When combined with infectious diseases, it can result in a low height-for-age ratio and/or nutritional dwarfing. Paradoxically, nutritional dwarfing may also be seen in children with excess weight for height.

One hundred and thirty-nine Peruvian children, ages 6 months to 5 years, with nutritional dwarfing

but excess weight for height, were studied using both total body water measurements and detailed anthropometric assessment. Results of this study were compared with the National Center for Health Statistics (NCHS) Reference Standards. The mean weight-for-length/height of children in the study sample was above the 50th percentile and appeared to increase with age. In contrast, the

*continued on page 14*

### Body Composition of Peruvian Children

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mean length/height-for-age fell from the 35th percentile by age 18 months and remained consistently low. Although arm muscle area, based on age and body weight, was not altered, anthropometric assessment revealed a lower body fat content (based on tricep skin-fold, subscapular skin-fold, and arm fat measurements). Additionally, greater values on assessment of total body water suggested a lower body fat content in these children.

Trowbridge FL, Marks JS, deRomana GL, et al. *Am J Clin Nutr* 1987;46:411.

**Editor's comment**—This interesting paper identifies nutritional dwarfing among children with ex-

cess body weight for length or height. The data show that undernourished children may cease to grow even before fat stores or lean body mass is depleted. This cessation may occur without weight loss or even when body weight continues to increase with age. Unfortunately, the authors did not provide data on progression of weight for age. It is possible that weight increments also slowed and the rate of advancement decreased, but since these changes were not as marked as those for length or height, a higher body weight for height continued. Additionally, these data emphasize the importance of repeated measurements of growth over time as indicators of normal health and nutrition. Any single weight-for-height measurement may fail to identify children with nutritional dwarfing.

The authors did not explain the causes of nutritional dwarfing in children without weight deficits. Dietary inadequacies beyond caloric or protein deficits may be implicated. For example, deficiencies of specific nutrients such as zinc and iron could lead to nutritional dwarfing. Additionally, obese children on weight-reduction diets also exhibit impaired growth despite continued excessive weight for height. Therefore, nutritional dwarfing in these Peruvian children may have resulted from a period of inappropriate diet following adequate nutrition. Stunting of growth without loss of body weight, but with reduction in body fat content, may occur as a gradual adjustment to inadequate dietary intake. Growth slows as an adaptive response to balance energy intake and expenditures.

Fima Lifshitz, M.D.

### Adolescent Growth and Pubertal Progression in the Silver-Russell Syndrome

Davies et al categorized the pattern of growth and development of 18 adolescents with Silver-Russell syndrome. All exhibited the classic features of the syndrome, including clinodactyly, triangular facies, and low-set ears. They had grown less than 1 cm in the previous year and had had their growth measured for at least 3 years prior to the onset of puberty. When attempting to describe a mean growth curve for these individuals, the authors paid special attention to the phase effect, ie, variability in timing, duration, and intensity of the adolescent growth spurt. Mathematical modeling utilizing the method of Preece and Baines was applied to the longitudinal data for each child. The age of attainment of pubertal stages was reported for each child as well.

In both males and females, the adult height was well below the third percentile for normal British

children. The standard deviation scores for adult height were -3.61 for boys and -3.58 for girls. However, subjects of both sexes exhibited height velocity curves that were well within the range of normal British children. No abnormal pattern or timing of pubertal events, including the pubertal growth peak height velocity, was observed. The actual peak height velocity was 8.3 cm per year in boys and 8.0 cm per year in girls. In addition, the age at the beginning of the adolescent growth spurt and the velocity at that time were also within normal ranges. The actual growth curve for these individuals with Silver-Russell syndrome demonstrates that there is little catch-up growth during childhood and adolescence, and that growth essentially proceeds normally in childhood. The mean age for the attainment of each stage of pubertal development and the mean age of menarche were also within normal range for British children. Thus, the authors conclude that there is normal pubertal development of sexual characteristics in those with the

Silver-Russell syndrome.

Davies P, Valley R, Preece M. *Arch Dis Child* 1988;63:130-135.

**Editor's comment**—This report is one of the first that carefully evaluates a number of individuals with Silver-Russell syndrome who have reached physical maturity. The growth curves that have been constructed for these children should be reviewed by pediatric endocrinologists. They are remarkably parallel to those for normal British children and the velocity curves fall well within the normal height velocity curves for British children as well. This careful characterization of children with Silver-Russell syndrome reemphasizes their poor prognosis with regard to adult stature but reassures that puberty is essentially normal in terms of the adolescent growth spurt and the development of sexual characteristics. Future long-term trials of growth-promoting agents will be required to see if there is to be any hope of catch-up growth in these children.

Robert M. Blizzard, M.D.

## Quantitation of Urinary GH in Children With Normal and Abnormal Growth

Albini et al have reevaluated the use of urinary growth hormone (GH) determinations as a screening test for GH deficiency (GHD) in children. Previous studies attempting to quantitate GH in the urine had not been successful because the assays were not sufficiently sensitive, and interfering substances found in the urine led to overestimation of GH excretion. In their study, the authors used a modification of the Hanssen procedure in which after urine is dialyzed and then lyophilized, GH is measured in a double-antibody radioimmunoassay (RIA).

This RIA uses polyclonal antibodies and standards obtained from the National Hormone and Pituitary Program. The intraassay and interassay coefficients of variation for GH antibodies and standards are 2.1 and 4.0, respectively, and the lower threshold of sensitivity of the assay is 0.15 ng/mL. High-pressure liquid chromatography (HPLC) studies confirmed the authenticity of urinary GH, as the elution profile of urinary GH was identical to both biosynthetic and pituitary GH standards. Furthermore, the HPLC fractions were assayed using a double-monoclonal immunoradiometric assay (IRMA) technique that recognizes only intact GH. The immunoreactive GH profiles defined by the two assays RIA and IRMA were identical. Recovery experiments were performed by adding known amounts of standard human GH to 50-mL aliquots of urine from GH-deficient subjects. The recovery of exogenous GH ranged from 80% to 100%.

Clinical studies were then performed to determine GH excretion in 82 children. These children were divided into three groups. Group 1 included 31 healthy children (ages 3-17 years) whose height was between the 5th and 95th percent-

iles. Nineteen were prepubertal and 12 were pubertal. Group 2 was composed of 21 children (ages 5-15 years) with GHD that had been determined by standard stimulation tests. Eleven of these children were prepubertal and ten were pubertal. Group 3 was composed of 30 children (ages 10-18 years) with idiopathic growth failure. Fifteen of these children were prepubertal and 15 were pubertal. Their heights were more than two standard deviations below the mean for age, and their growth rates were less than 4 cm/year. However, their peak GH responses to two or more stimulation tests were greater than 8 ng/mL. Overnight urines (6 P.M.-8 A.M.) were collected and refrigerated prior to GH analysis. GH excretion was standardized for body weight and expressed as ng/kg/12 hours as well as in terms of body surface area (ng/m<sup>2</sup>/12 hours). In addition, GH excretion was standardized in terms of creatinine excretion (ng/g of creatinine).

When urinary GH excretion was expressed in terms of body weight or body surface area, the secretion was significantly greater in group 1 than group 2 or group 3. In addition, children in group 2 excreted significantly lower amounts of GH than those in group 3. However, when the data were expressed in terms of creatinine excretion, the differences in GH excretion between group 2 (GH-deficient subjects) and group 3 (children with idiopathic growth failure) were not significant. Prepubertal and pubertal children in each of the three groups excreted similar amounts of GH regardless of the method of standardization. The authors conclude that measurement of urinary GH may prove to be useful in screening patients with suspected GHD. This clinical methodology is significantly easier for staff and patients and less costly than serial blood sampling over 24 hours in determining GH neurosecretory dysfunction. However, approxi-

mately 50% of the children with idiopathic growth failure had urinary GH values that were similar to those of children with classic GHD, leading the authors to suggest that these children may have GHD.

Albini C, Quattrin T, Vandlen R, et al. *Pediatr Res* 1988;23:89-92.

**Editor's comment**—The studies reported above were carefully performed and show significantly more precision than previously reported evaluations of urinary GH excretion. The documentation of the authenticity of urinary GH by this very sensitive assay is reassuring. However, the fact that 50% of the children with idiopathic growth failure had urinary GH values similar to those of children with classic GHD suggests that further studies are still required in approximately half of the children who had abnormal urinary GH values prior to the initiation of therapy with exogenous GH. In addition, since there were no differences in the excretion of urinary GH between prepubertal and pubertal children in each of the three groups, the question remains as to whether some of the children with idiopathic growth failure and abnormally low urinary GH values, in fact, had constitutional delay of growth and adolescence. The present study, however, should encourage others to obtain more data utilizing the reported procedure in an attempt to fully define its utility as a screening process for GHD. Clearly, the availability of a noninvasive, low-cost screening procedure for GHD would be welcomed by most pediatric endocrinologists.

William L. Clarke, M.D.

**Address for Correspondence**  
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## MEETING CALENDAR

**April 12-16, 1989** 15th Training Course on Hormonal Assay Techniques. Holiday Inn, Bethesda, Maryland. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

**April 27-30, 1989** Lawson Wilkins Pediatric Endocrine Society Review Course in Pediatric Endocrinology. Hyatt Regency Washington on Capitol Hill, Washington, D.C. Contact: Beverly Wellman, Serono Symposia, USA, 280 Pond Street, Randolph, MA 02368 (800-225-5185)

**April 27-30, 1989** Biennial Meeting of the Society for Research in Child Development. Kansas City, Missouri. Contact: Kathleen McCluskey-Fawcett, Ph.D., Department of Psychology, University of Kansas, 426 Fraser Hall, Lawrence, KS 66045-2160 (913-864-4131)

**May 1-5, 1989** Annual Meeting of the American Pediatric Society/Society for Pediatric Research/Ambulatory Pediatric Association. Washington Sheraton, Washington, D.C. Contact: Debbie Wogenrich, Executive Director, Society for Pediatric Research, 2650 Yale Boulevard S.E., Suite 104, Albuquerque, NM 87106 (505-764-9099)

**May 5, 1989** Annual Meeting of the Lawson Wilkins Pediatric Endocrine Society. Washington Sheraton, Washington, D.C. Contact: Gilbert August, M.D., Department of Endocrinology, Children's Hospital, National Medical Center, 111 Michigan Avenue N.W., Washington, D.C. 20010 (202-745-2121)

**June 3-6, 1989** Annual Meeting of the American Diabetes Association. Detroit, Michigan. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314 (703-549-1500 or 800-ADA-DISC)

**June 21-24, 1989** 71st Annual Meeting of the Endocrine Society. Seattle Convention Center, Seattle, Washington. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

**September 26-28, 1989** 30th Annual Meeting of the American College of Nutrition. Omni International Hotel, Norfolk, Virginia. Contact: Kay Balun, Administrative Assistant, American College of Nutrition, 345 Central Avenue, Suite 207, Scarsdale, NY 10543 (914-723-4247)

**October 11-14, 1989** 41st Annual Postgraduate Assembly of The Endocrine Society. Fairmont Hotel, New Orleans, Louisiana. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

**October 29-November 3, 1989** Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology (scientific sessions, October 30-November 1). Jerusalem Hilton, Jerusalem, Israel. Contact: Zvi Laron, M.D., Beilinson Medical Center, Petah Tikva 49 100 Israel

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